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The Archives of Internal Medicine

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A STUDY OF URIC ACID IN GOUT*

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"Without uric acid, no gout," has been for many years a generally accepted dictum. And yet in spite of many investigations the relation of uric acid to gout has not been clearly established. In the diagnosis of gout by chemical means the same uncertainty exists. The uric acid may be increased in the blood and diminished in the urine, but the diagnostic value of these findings is doubtful. The development of new methods in biochemistry within the past few years permits a more thorough study of the factors governing the excretion of uric acid, and for this reason we have reinvestigated this subject.

Our studies on gout have been along the following four lines:

1. A comparison of the uric acid content of the blood in the gouty and in the nongouty.

2. The results obtained by the intravenous injections of uric acid in the gouty and in the nongouty.

3. A comparison of the exogenous output of uric acid by the gouty and the nongouty in feeding experiments.

4. The functional condition of the kidneys in gout. (This will be published as a separate study.)

I. THE URIC ACID CONTENT OF THE BLOOD

In 1913 Folin and Denis[1] introduced a colorimetric method for the determination of uric acid in small quantities of blood. Since our investigations were begun Folin has offered certain criticisms of his own method. Nevertheless, by its use data have been obtained which are of clinical interest in relation to gout. Different observers have

* Submitted for publication May 15, 1917.

* From the Medical Clinic of the Peter Bent Brigham Hospital.

1. Folin, O., and Denis, W.: A New Colorimetric Method for the Determination of Uric Acid in the Blood. Jour. Biol. Chem., 1913, **13,** 469.

Pratt, J. H.: A Study of Uric Acid in the Blood in Gout by the Method of Folin and Denis. Tr. Assn. Am. Phys., 1913, **28,** 387.

used modifications of the Folin and Denis method, but their reported figures in general seem too high to be comparable with those obtained by the use of the original method. For this reason we have not quoted the work of these authors, but only that of those using the method described by Folin and Denis.

The Uric Acid Content of the Blood in Nongouty Persons.—Figures for the quantities of uric acid estimated by the Folin and Denis method in the bloods of 381 nongouty persons have been collected from the literature.[2] In 314, or 82 per cent., the amounts of uric acid per 100 c.c. of blood ranged from 0.5 to 3.0 mg. Twenty of the latter number were normal persons, while the remainder represented cases of various organic disease, exclusive of gout, or cases with psychopathic conditions. Folin and Lyman[3] found 4 mg. of uric acid in the blood of a healthy man who gave a family history of gout. Whether or not this patient should be grouped here as nongouty is a question of doubt. The amounts of urea and nonprotein nitrogen in the blood of this person were normal, so that there is no evidence for renal impermeability to other nitrogenous substances. Of the 156 psychopathic patients reported by Adler and Ragle[4] the blood of thirty eight contained from 2.0 to 4.5 mg. of uric acid per 100 c.c. The number in which more than 3 mg. was present is not stated. Whether or not any of the cases were gouty or nephritic is not reported.

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2. Folin, O., and Lyman, H.: On the Influence of Phenylquinolin Carbonic Acid (Atophan) on the Uric Acid Elimination. Jour. Pharmacol. and Exper. Therap., 1913, **4,** 539.

McLester, J. S.: Studies on the Uric Acid of the Blood and Urine with Special Reference to the Influence of Atophan. THE ARCHIVES INT. MED., 1913, **12,** 739.

Folin, O., and Denis, W.: On the Uric Acid, Urea, and total Nonprotein Nitrogen in Human Blood. Jour. Biol. Chem., 1913, **14,** 29.

Folin, O., and Denis, W.: On the Creatinin and Creatin Content of Blood. Jour. Biol. Chem., 1914, **17,** 487.

Kocher, A. R.: Ueber den Harnsäuregehalt des Blutes als Krankheitssymptom. Deutsch. Arch. f. klin. Med., 1914, **115,** 380.

Adler, H., and Ragle, B.: A Note on the Increase of Total Nitrogen and Urea Nitrogen in the Cerebrospinal Fluid in Certain Cases of Insanity, with Remarks on the Uric Acid Content of the Blood. Boston Med. and Surg. Jour., 1914, **171,** 769.

Folin, O., and Denis, W.: The Diagnostic Value of Uric Acid Determinations in Blood. THE ARCHIVES INT. MED., 1915, **16,** 33.

Pratt, J. H.: Studies on the Uric Acid in the Blood in Gout. Am. Jour. Med. Sc., 1916, **151,** 92.

3. Folin, O., and Lyman, H.: See Footnote 2.

4. Adler, H., and Ragle: Boston Med. and Surg. Jour., 1914, **171,** 769. See Footnote 2.

The bloods of the remaining sixty-seven, or 17.6 per cent., of the 381 nongouty persons contained from 3.0 to 10.0 mg. per 100 c.c. The diagnoses of these cases were:

I. Chronic nephritis with and without uremia.[5]

II. Arterial hypertension.[6]

III. Acute and chronic types of nongouty and nontraumatic arthritis.[7]

IV. Chronic lead poisoning.[8]

V. Leukemia.[9]

VI. Malignancy.[10]

VII. Acute infections, especially lobar pneumonia.[11]

VIII. One case each of migraine,[10] of renal calculus,[12] without nephritis, of mitral stenosis,[13] and of puerperal toxemia[14] in which the condition of the kidneys is not stated.

Obviously, the results obtained in the first three groups, which include nephritis and arthritis, are of most importance in determining the value of uric acid estimations in the blood as a means of differential diagnosis in gout. All cases of nephritis[15] or of arthritis[16] do not retain uric acid, in spite of the fact that in both conditions the blood may contain large amounts of nonprotein nitrogenous substances. Whether or not nephritis was present in the cases of arthritis in which retention of nonprotein nitrogen occurred in the blood, is not stated.

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5. Folin, O., and Lyman, H.: Jour. Pharmacol. and Exper. Therap., 1913, **4,** 539. Folin, O., and Denis, W.: Jour. Biol. Chem., 1913, **14,** 29. Kocher, A. R.: Deutsch. Arch. f. klin. Med., 1914, **115,** 380. Folin, O., and Denis, W.: THE ARCHIVES INT. MED., 1915, **16,** 33. See Footnote 2.

6. McLester, J. S.: THE ARCHIVES INT. MED., 1913, **12,** 739. See Footnote 2.

7. Folin, O., and Denis, W.: Jour. Biol. Chem., 1914, **17,** 487. Kocher, A. R.: Deutsch. Arch. f. klin. Med., 1914, **115,** 380. Folin, O., and Denis, W.: THE ARCHIVES INT. MED., 1915, **16,** 33. Pratt, J. H.: Am. Jour. Med. Sc., 1916, **151,** 92. See Footnote 2.

8. Folin, O., and Lyman, H.: Jour. Pharmocol. and Exper. Therap., 1913, **4,** 539. Folin, O., and Denis, W.: Jour. Biol. Chem., 1913, **14,** 29. See Footnote 2.

9. Folin, O., and Denis, W.: Jour. Biol. Chem., 1913, **14,** 29. Kocher, A. R.: Deutsch. Arch. f. klin. Med., 1914, **115,** 380. See Footnote 2.

10. Kocher, A. R.: Deutsch. Arch. f. klin. Med., 1914, **115,** 380. See Footnote 2.

11. Folin, O., and Denis, W.: Jour. Biol. Chem., 1914, **17,** 487. Kocher, A. R.: Deutsch. Arch. f. klin. Med., 1914, **115,** 380. Folin, O., and Denis, W.: THE ARCHIVES INT. MED., 1915, **16,** 33.

12. Folin, O., and Denis, W.: Jour. Biol. Chem., 1913, **14,** 29.

13. Folin, O., and Lyman, H.: Jour. Pharmacol. and Exper. Therap., 1913, **4,** 539.

14. Folin, O., and Denis, W.: Jour. Biol. Chem., 1914, **17,** 487.

15. Folin, O., and Denis, W.: Jour. Biol. Chem., 1913, **14,** 29.

16. Folin, O., and Denis, W.: THE ARCHIVES INT. MED., 1915, **16,** 33.

Of thirty-nine reported cases of nongouty, nontraumatic arthritis[7] the blood uric acid varied between 1.2 and 2.7 mg. in thirty, or 77 per cent., and from 3.0 to 7.6 mg. in nine, or 13 per cent. In one of these cases[17] the figures varied from 1.6 to 5.0 mg. and in another from 0.8 to 7.6 mg. Twenty, or 42 per cent., of fifty reported cases of nephritis[18] showed from 1.0 to 2.9 mg. of uric acid per 100 c.c. of blood, and twenty-nine, or 58 per cent., from 3.3 to 10.0 mg. All of the above patients were receiving a purin-free diet at the time of the blood examinations.

Using the methods of Folin and Denis, we have determined the uric acid and the total nonprotein nitrogen in the blood of eight nongouty patients without clinical evidences of nephritis and in one case of advanced chronic nephritis. The findings are given in Table 1.

TABLE 1.—Uric Acid Content of Blood of Nongouty Patients

Case	Diagnosis	Mg. Uric Acid per 100 C.c. Blood	Mg. Nonprotein Nitrogen per 100 C.c. Blood	Diet of Patient
1	Dementia praecox	2.1	42	Purin-free
2	Dementia praecox	1.6-2.5	42	Purin-free
3	Senile dementia	0.8	39	Purin-free
4	Chronic nephritis, chronic arthritis	4.5	137	Purin-free
5	Chronic arthritis	2.2	...	Mixed
6	Chronic arthritis	2.4-3.3	32	Purin-free
7	Acute gonorrheal arthritis	2.0	40	Mixed
8	Chronic arthritis	1.8	28	Purin-free
9	Cirrhosis of the liver	1.7	40	Purin-free

The case of nephritis gave a high value for the blood uric acid. One of the cases of dementia praecox and one of chronic arthritis showed 3.5 and 3.3 mg. per 100 c.c. of blood, but on another examination less than 3 mg. were found. Our results agree with those collected from the literature and confirm the observation that the blood of the great majority of nongouty persons contains less than 3.0 mg. of uric acid per 100 c.c.

The Uric Acid Content of the Blood in Gouty Patients.—Of forty-nine reported cases of gout in which the uric acid in the blood was estimated by the method of Folin and Denis, thirty-eight, or 86.3 per

17. Pratt, J. H.: Am. Jour. Med. Sc., 1916, **151,** 92.

18. Folin, O., and Lyman, H.: Jour. Pharmacol. and Exper. Therap., 1913, **4,** 539. McLester, J. S.: The Archives Int. Med., 1913, **12,** 739. Folin, O., and Denis, W.: Jour. Biol. Chem., 1913, **14,** 29. Folin, O., and Denis, W.: Jour. Biol. Chem., 1914, **17,** 487. Folin, O., and Denis, W.: The Archives Int. Med., 1915, **16,** 33.

cent.,[19] showed from 3.1 to 7.2 mg. per 100 c.c., and six[20] from 1.7 to 2.8 mg. All but six of the patients were on a purin-free diet prior to the uric acid determinations. In these six the blood contained from 3.1 to 5.2 mg. of uric acid per 100 c.c. of blood. Chronic nephritis was diagnosed in but two[21] of the entire number of patients. In these the blood contained 3.1 to 5.7 mg. of uric acid. In seventeen of the cases[22] the nonprotein nitrogen in the blood was determined. Less than 36 mg. were found in five, or 29.4 per cent., and 52 to 60 mg. in two, or 11.8 per cent.

Using the methods of Folin and Denis, we have determined the uric acid and nonprotein nitrogen content of the blood in the accompanying tabulated seven patients with gout (Table 2). All of these patients possessed tophi. Two were also suffering with chronic nephritis. The presence of nephritis was questionable in the other five patients, the only evidences being an occasional very slight trace of albumin or a scanty number of hyaline or finely granular casts. In one of the five patients cardiovascular disease was present.

TABLE 2.—URIC ACID CONTENT OF THE BLOOD IN GOUTY PATIENTS

Case	Mg. Uric Acid per 100 C.c. Blood	Mg. Nonprotein Nitrogen per 100 C.c. Blood	Diet of Patient
1*	5.1 4.8	.... 57.0	Purin-free
2*	3.2	62.0	Purin-free
3	4.6 3.5	.... 53.0	Purin-free
4	3.3	50.0	Purin-free
5	5.1 4.3	.... 29.0	Purin-free
6	4.9	43.6	Purin-free
7	5.8	47.6	Mixed

* Patient had chronic nephritis.

More than 3 mg. of uric acid per 100 c.c. of blood were found in all cases. The nonprotein nitrogen of the blood was increased definitely above 50 mg. per 100 c.c. in the two patients with nephritis, No relation was found to exist between the amount of uric acid and the quantity of nonprotein nitrogenous substances in the blood. A

19. See Footnote 2.

20. Kocher, A. R.: Deutsch. Arch. f. klin. Med., 1914, **115,** 380. Pratt, J. H.: Am. Jour. Med. Sc., 1916, **151,** 92.

21. Kocher, A. R.: Deutsch. Arch. f. klin. Med., 1914, **115,** 380. Folin, O., and Denis, W.: THE ARCHIVES INT. MED., 1915, **16,** 33.

22. Folin, O., and Lyman, H.: Jour. Pharmacol. and Exper. Therap., 1913, **4,** 539. Folin, O., and Denis, W.: THE ARCHIVES INT. MED., 1915, **16,** 33.

review of the literature[22] gives the same findings. The results obtained by our studies confirm the observations of previous writers[16] and show that although in the majority of gout cases there are increased amounts of uric acid in the blood, a large percentage do not have markedly increased quantities of other nonprotein nitrogenous substances in their blood when on a purin-free diet.

We appreciate that the status of the method for estimating blood uric acid is unsettled. Nevertheless, on statistical evidence more than 3 mg. of uric acid per 100 c.c. of blood is a symptom of gout and is of especial importance when less than 50 mg. of nonprotein nitrogen is present.

II. EFFECTS OF INTRAVENOUS INJECTIONS OF URIC ACID

We have studied the effect of the intravenous injection of 0.5 gm. of uric acid on the quantities of that substance in the blood and in the urine. The method of procedure was to obtain the endogenous level of uric acid in the urine after the patients had been on a purin-free diet. Then the injection was made. Quantitations of uric acid in the blood were made on samples taken a few minutes prior to the injection, four hours afterwards, and then at twenty-four-hour periods. Estimations of the urinary uric acid were made in urine collected in several periods during the day of the injection and thereafter in urine collected for twenty-four-hour periods. The diet and analytical methods used are as follows:

Methods.—Patients were placed on a purin-free diet at least seven days before the injections of uric acid were made. The diet consisted of bread, cauliflower, potatoes, rice, cornflakes, the cereal preparations of wheat, lettuce, cabbage, tapioca, jelly, cream, butter, cheese, eggs, and sugar.

For purposes of injection 0.5 gm. of uric acid was dissolved in 30 c.c. of distilled water with the aid of 1 gm. of piperazine. The solution was sterilized in the autoclave at 10 pounds pressure for five minutes. It was found that autoclaving the solution for fifteen minutes under a pressure of 20 pounds of steam did not decompose the uric acid. Uric acid in the blood was determined by the original method of Folin and Denis[1] or by their modified procedure.[23] Nonprotein nitrogen was determined by either the original method of Folin and Denis[24] or by their later direct Nesslerization procedure.[25] Uric acid in the urine was quantitated by one of Folin's colorimetric methods:[26] In certain cases determinations were made with the uric acid phenol reagent by the method described in Folin's laboratory manual.[23] In other cases his uric acid reagent was substituted for the uric acid phenol reagent in this method. The latter reagent gives at times results which are slightly too high. Neverthe-

23. Folin, O.: Laboratory Manual of Biological Chemistry, New York, 1916.

24. Folin, O., and Denis, W.: New Methods for the Determination of Total Nonprotein, Urea and Ammonia in the Blood. Jour. Biol. Chem., 1912, **11,** 527.

25. Folin, O., and Denis, W.: Nitrogen Determinations by Direct Nesslerization. Nonprotein Nitrogen in Blood. Jour. Biol. Chem., 1916, **26,** 491.

26. Folin, O., and Denis, W.: On the Colorimetric Determination of Uric Acid in the Urine. Jour. Biol. Chem., 1913, **14,** 95.

less, we found that after feeding sweetbreads the results obtained in the same persons with the uric acid phenol reagent were fully comparable to those obtained with the uric acid reagent. In the descriptive tables, methods employed to quantitate uric acid will be designated in a footnote as the original method, the uric acid reagent method, and the uric acid phenol reagent method.

Intravenous Injections of Uric Acid Into Nongouty Persons.— Studies by previous observers on the excretion of uric acid in nongouty persons after its intravenous injection are given in Table 3. The experimental subjects were all on a purin-free diet.

TABLE 3.—PREVIOUS OBSERVATIONS ON THE EXCRETION OF INTRAVENOUSLY INJECTED URIC ACID BY NONGOUTY PERSONS

Observer	Diagnosis*	Exogenous Output of Uric Acid		Duration in Days of the Exogenous Output	Amount of Uric Acid Injected, Gm.
		Gm.	Per Cent.		
Bürger and Schweriner[23]	1. Chronic arthritis	0.66	132	3	0.5
	2. Chronic arthritis	0.89	178	3	0.5
	3. Chronic arthritis	0.38	76	1	0.5
Umber and Retzlaff[27]	3. Normal	0.40	80	4	0.5
	4. Normal	0.47	95	2	0.5

* The urine findings were normal in all instances.

Table 3 shows that after the intravenous injections into five nongouty persons the amounts of uric acid excreted varied. In two of the three cases of arthritis more uric acid was excreted than had been injected.

We have given five nongouty persons intravenous injections of 0.5 gm. of uric acid. Three of these were insane persons, and two had chronic arthritis. No evidence of kidney lesions was present in these patients, although complete renal function studies were made on but one. The findings of the uric acid injection experiments are given in the following protocols.

(PROTOCOLS FOLLOW)

PROTOCOLS

CASE 1.—J. M., Med. No. 5948, white, male, aged 32.

Diagnosis: Dementia praecox.

The patient did not use alcohol. The physical examination was negative. Blood pressure was 100 mm. systolic and 70 mm. diastolic. The urine examination was negative. Phthalein excretion was 60 per cent. in two hours. The patient was placed on a purin-free diet Oct. 29, 1915.

Date	Time of Collection	Urine			Blood		Remarks
		Amount in C.c.	Uric Acid in Gm.	Creatinin in Gm.	Non-protein N in Mg. per 100 C.c.	Uric Acid in Mg. per 100 C.c.	
Nov. 1-2	9 - 9 a.m.	1,570	0.50	1.20			
2-3	9 - 9 a.m.	1,820	0.50	0.97			
3-4	9 - 9 a.m.	2,810	0.61	1.26			
4-5	9 - 9 a.m.	3,905	0.54	1.21			
5	9 a.m. - 12 N.	370	0.08				
	12:15 p.m.	.....	....	....	.....	3.50	0.5 gm. uric acid intravenously
	12 N. - 4 p.m.	280	0.09				
	4:15 p.m.	.....	....	....	.....	2.90	
5-6	4 p.m. - 12 N.	935	0.43				
	12 N. - 12 N.	1,215	0.54	0.98			
6	4:15 p.m.	.....	....	....	42.00	2.10	
6-7	12 N. - 12 N.	2,420	0.71	1.25			
7	4:15 p.m.	.....	....	....	.....	1.70	
7-8	12 N. - 12 N.	2,550	0.66	1.37			
8	4:15 p.m.	.....	....	....	.....	2.50	
8-9	12 N. - 12 N.	2,250	0.66	1.06			
9	4:15 p.m.	.....	....	....	.....	1.6	

Endogenous output of uric acid, November 2 to 5 = 2.15 gm.
Endogenous output of uric acid per day = 0.54 gm.
Per cent. of injected uric acid excreted = 82 per cent.
Uric acid determinations made by the original method.

CASE 2.—E. S., Med. No. 5510. White, male, aged 41.

Diagnosis: Dementia praecox.

The patient was not an alcoholic. The physical examination was negative. Blood pressure was 140 mm. systolic and 95 mm. diastolic. The urine examination was negative. Phthalein excretion was 65 per cent. in two hours. The patient was placed on a purin-free diet on Oct. 29, 1915.

Date	Time of Collection	Urine			Blood		Remarks
		Amount in C.c.	Uric Acid in Gm.	Creatinin in Gm.	Non-protein N in Mg. per 100 C.c.	Uric Acid in Mg. per 100 C.c.	
Nov. 1-2	9 - 9 a.m.	1,595	0.71	1.77			
2-3	9 - 9 a.m.	2,525	0.69	1.31			
3-4	9 - 9 a.m.	2,415	0.78	1.50			
4-5	9 a.m. - 7 a.m.	2,680	0.56	1.50			
5	7 a.m. - 9 a.m.	400	0.08	0.14			
	9 a.m. - 12 N.	180	0.09	0.13			
	12:15 p.m.	.....	....	....	.....	2.10	0.5 gm. uric acid intravenously
	12 N. - 4 p.m.	1,180	0.31	0.31			
	4:15 p.m.	.....	....	....	.....	2.80	
5-6	4 p.m. - 12 N.	1.585	0.65	1.05			
	12 N. - 12 N.	2,765	0.96	1.36	.....	1.90	Total amount for 24 hours
6	4:15 p.m.	.....	....	....	.....	1.20	
6-7	12 N. - 12 N.	2,505	0.93	1.60			
7	4:15 p.m.	.....	....	1.70	.....	1.70	
7-8	12 N. - 12 N.	3,016	0.87	1.88			
	4:15 p.m.	.....	....	....	42.00	2.50	
8-9	.....	1,280	0.49	1.11			
9	4:15 p.m.	.....	....	....	.....	1.6	

Endogenous output of uric acid November 2 to 5 = 2.74 gm.
Endogenous output of uric acid per day = 0.69 gm.
Exogenous output of uric acid November 6 to 8 = 0.69 gm.
Per cent. of injected uric acid excreted = 138 per cent.
Uric acid determinations were made by the original method.

CASE 3.—M. K., Med. No. 5708. White, female, aged 73.

Diagnosis: Psychoneurosis.

The patient was not an alcoholic. The physical examination was negative except for evidences of arteriosclerosis usual for the age. Blood pressure was 130 mm. systolic and 65 diastolic. The urine contained the slightest possible trace of albumin with the heat and nitric acid tests, and enough pus to render it turbid in appearance. Phthalein excretion was 55 per cent. in two hours. The patient was placed on a purin-free diet on Oct. 29, 1915.

Date	Time of Collection	Urine			Blood		Remarks
		Amount in C.c.	Uric Acid in Gm.	Creatinin in Gm.	Non-protein N in Mg. per 100 C.c.	Uric Acid in Mg. per 100 C.c.	
Oct. 31 - Nov. 1	7 a.m. - 7 a.m.	2,035	0.32	0.89			
1-2	7 a.m. - 7 a.m.	1,130	0.29	0.54			
2-3	7 a.m. - 7 a.m.	1,194	0.36				
3-4	7 a.m. - 7 a.m.	1,048	0.21	0.58			
4	7 a.m. - 10 a.m.	220	0.05				
	10 a.m. - 12 N.	204	0.06				
	12 N.	.....	....	....	.....	0.8	
	12 N.	.....	....	....	.....	....	0.5 gm. uric acid intravenously
	12 N - 4 p.m.	167	0.01				
	4 p.m.	.....	....	....	.....	2.9	
4-5	4 p.m. - 7 a.m.	920	0.32				
5	7 a.m. - 12 N.	340	0.19				
4-5	12 N. - 12 N.	1,427	0.52	0.54			
5	4 p.m.	.....	....	....	.. ..	1.4	
5-6	12 N. - 12 N.	1,530	0.40	0.57			
6	4 p.m.	.....	....	....	29.2	0.8	
6-7	12 N. - 12 N.	1,920	0.32	0.61			
7-8	12 N. - 12 N.	1,350	0.22	0.56			

Endogenous output of uric acid November 1 to 4 = 1.18 gm.
Endogenous output of uric acid per day = 0.30 gm.
Exogenous output of uric acid November 5 to 6 = 0.32 gm.
Per cent. of injected uric acid excreted = 64 per cent.
Uric acid determinations were made by the original method.

CASE 4.—M. T. Mc., Med. No. 3415. White, female, aged 39.

Diagnosis: Chronic arthritis.

The patient's habits were good. Except for the joint changes of a chronic arthritis, the physical examination was negative. Blood pressure was 103 mm. systolic and 85 mm. diastolic. The urine contained the slightest possible trace of albumin and a small amount of pus microscopically.

Date	Time of Collection	Urine			Blood		Remarks
		Amount in C.c.	Uric Acid in Gm.	Creatinin in Gm.	Non-protein N in Mg. per 100 C.c.	Uric Acid in Mg. per 100 C.c.	
Sept. 16	.....	.....	....	....	.....	....	Purin-free diet begun
23	.....	.....	....	....	22.20	2.4	
Oct. 5-6	7 a.m. - 7 a.m.	2,190	0.34	0.88			
6-7	.....	2,810	0.23	0.99			
7-8	.....	1,320	0.30	1.05			
8-9	.....	1,575	0.22	0.98			
9	7 a.m. - 10 a.m.	440	0.08				
	1:20 p.m.	.....	....	....	.....	3.2	
	1:30 p.m.	.....	....	....	.....	....	0.5 gm. uric acid intravenously
	10 a.m. - 12 N.	400	0.02	0.08			
	12 N. - 4 p.m.	440	0.10	0.17			
	6 p.m.	.....	....	....	.....	4.1	
9-10	4 p.m. - 7 a.m.	1,000	0.26	0.53			
10	2 p.m.	.....	....	....	.....	3.9	
9-10	12 N. - 12 N.	2,200	0.42	0.79	.....	....	Total for 24 hrs.
10-11	7 - 7 a.m.	1,000	0.20	0.84			
11	2 p.m.	.....	....	....	.....	2.8	
11-12	.....	1,715	0.22	0.89			
12	.....	.....	....	....	.....	2.9	

Endogenous output of uric acid October 6 to 9 = 1.24 gm.
Endogenous output of uric acid per day = 0.31 gm.
Exogenous output of uric acid October 10 = 0.11 gm.
Per cent. of injected uric acid excreted = 22 per cent.
Uric acid determinations were made by the original method.

CASE 5.—W. H. K. Med. No. 5278. White, female, aged 29.

Diagnosis: Chronic arthritis.

The patient's habits were good. She had had chronic polyarthritis with occasional fairly acute exacerbations for the previous two years. The joints had never been either severely painful or tender. During the previous six months stiffness of the knees had prevented walking. Physical examination was negative except for the joints. There was limitation of motion and crepitation in all joints of the extremities. The elbows, wrists, finger joints, knees, and joints of both halluces were enlarged, principally as the result of thickening of the periarticular tissues. Blood pressure was 110 mm. systolic and 75 mm. diastolic. Urine examinations were negative except for a scant trace of albumin and a rare cast in one of the specimens. Phthalein excretion was 65 per cent. in two hours.

Date	Time of Collection	Urine		Blood		Remarks
		Amount in C.c.	Uric Acid in Gm.	Nonprotein N in Mg. per 100 C.c.	Uric Acid in Mg. per 100 C.c.	
Oct. 31	.....	.....	....	.....	1.8	Purin-free diet begun
Nov. 4-5	7 a.m. - 7 p.m.	850	0.57			
5-6	.....	850	0.63			
6-7	.....	740	0.56			
7-8	.....	820	0.47			
8	7 a.m. - 10 a.m.	350	0.01			
	10 - 12 N.	100	0.06			
	12 N.	.....	....	.....	1.6	
	12:15 p.m.	.....	....	.....	....	0.5 gm. uric acid intravenously
	12 N. - 2 p.m.	297	0.18			
	2 - 5 p.m.	205	0.13			
	4:15 p.m.	.....	....	.....	2.5	
8-9	5 p.m. - 7 a.m.	297	0.19			
8-9	7 a.m. - 7 p.m.	1,240	0.57			
9	7 a.m. - 12 N.	278	0.16			
	12:15 p.m.	.....	....	27.9	1.5	
8-9	12 N. - 12 N.	1,177	0.66			
9-10	7 a.m. - 7 a.m.	988	0.41			
10-11	7 a.m. - 7 a.m.	1,210	0.55			
11-12	.....	1,045	0.75			
12-13	.....	975	0.57			
13-14	.....	1,170	0.61			

The daily output of uric acid was too variable to permit an accurate determination of an average endogenous level.

Endogenous output of uric acid November 5 to 8 = 2.23 gm.

Endogenous output of uric acid per day = 0.56 gm.

Exogenous output of uric acid November 9 = 0.10 gm.

Exogenous output of uric acid November 12 = 0.19 gm.

Per cent. of injected uric acid excreted November 9 = 20 per cent.

Per cent. of injected uric acid excreted November 12 = 38 per cent.

Total per cent. of injected uric acid excreted = 58 per cent.

Uric acid determinations were made by the uric acid phenol reagent method.

A study of the foregoing protocols shows a bizarre behavior in the output of the injected uric acid. Case 2 is the only one in which it is definitely apparent that the output of the exogenous uric acid began within the first four hours after its injection. The output began within the first twenty-four hours in Case 2, 3, 4 and 5. The excretion of the injected uric acid did not begin until during the second twenty-four-hour period after its administration in Case 1. In Case 5 the output of uric acid occurred in the first and fourth days following the injection. The excretion of the intravenously introduced uric acid was completed in from one to four days in all the above cases. In Case 1 determinations were stopped before the endogenous level in the urine had been reached. Thus there were great variations found both in the time of beginning and the duration of excretion of the injected uric acid.

The quantities of the intravenously injected uric acid which were excreted varied from 22 per cent. to 138 per cent. in the five cases. That a patient should excrete less than 100 per cent. of the amount of uric acid injected is explained by a loss occurring during the distribution throughout the body. Such a distribution must be necessarily undergone before the uric acid can reach the kidneys. As will be discussed later, other substances disappear from the blood after their intravenous injection. The output of more than 100 per cent. of the uric acid injected is only apparent. This is probably due to the variations commonly found in the daily endogenous amount of uric acid excreted. If the endogenous excretion has been low prior to the injection, and for the first few days following intravenous administration a higher endogenous output in the urine should be present, then the addition of a considerable amount of exogenous uric acid derived from that injected would make an apparent excretion of more than 100 per cent. It is to be noted that 0.1 gm. represents 20 per cent. of the amount of uric acid which was injected.

Our findings in the urine after the intravenous injection of uric acid into persons without gout show: (1) that the excretion may occur at irregular intervals; (2) that the starting of the excretion usually varies from a few hours to twenty-four hours; (3) that the percentage excreted ranges from very little to very much; and (4) that the duration of the output of injected uric acid is often protracted over several days.

The quantities of uric acid found in the blood after its intravenous injection varied in the different cases. In Case 1 no increase in the blood uric acid followed the injection. There was considerable fluctuation in the amounts present in this case. An increase in the blood uric acid was found four hours after the injection in Cases 2, 3, 4 and 5. This increase disappeared within the first twenty-four hours in Cases 2

and 5, but not until the second twenty-four hours after the injection in Cases 3 and 4.

Definite time relations between the disappearance of uric acid from the blood and its excretion in the urine cannot be established for non-gouty individuals from a study of the tables showing our results.

Intravenous Injections of Uric Acid into Gouty Persons.—Prior to our investigations, Umber and Retzlaff[27] had studied the output of intravenously injected uric acid in four patients with gout. In three the kidneys were stated to be normal. The percentages of uric acid excreted by these three patients were none, 8.6 per cent. and 24 per cent. within from one to two days. In their fourth case of gout the patient had "beginning albuminuria." In this case 23.6 per cent. of the injected uric acid was excreted within the first twenty-four hours. The results of this test in four cases have been published by Bürger and Schweriner.[28] One retained all the uric acid. The urine of this patient was free from albumin and casts. In the other cases small amounts were excreted. The urine of only one of these patients contained albumin and casts.

We have given four patients with gout intravenous injections of 0.5 gm. of uric acid. One patient had a severe type of nephritis. Of the others one showed no signs of nephritis and two such slight symptoms of that disease that kidney lesions could not be definitely diagnosed. The condition of the kidneys in these cases will be discussed in another communication on the study of the renal function in gout. The findings in the blood and urine after the uric acid injections are given in the following protocols.

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27. Umber and Retzlaff: Zur Harnsäure-Retention bei der Gicht. Verhandl. d. Kong. f. inn. Med., Wiesbaden, 1910, **27,** 436.

28. Bürger, M., and Schweriner, F.: Ueber das Verhalten intravenous einverleibten Glykokolls bei gesunden und krankheiten Menschen (mit besonderer Berücksichtigung der Gicht und Lebercirrhose). Arch. f. exper. Pathol. u. Pharmakol., 1913, **74,** 353.

CASE 6.—D. J. T., Med. No. 2963. White, male, aged 55.

Diagnosis: Acute and chronic gout; arteriosclerosis; chronic nephritis; hypertension; chronic myocarditis; angina pectoris.

The patient had used one pint of rum a day for many years. He had had five attacks of typical podagra in the metatarsophalangeal joint of the right hallux during the previous fifteen years. One attack occurred while he was under observation in the hospital. Physical examination showed that the heart was enlarged to the left. The radial artery walls were tortuous and sclerotic. Blood pressure was 184 mm. systolic and 140 mm. diastolic. The urine contained a trace of albumin and an occasional cast. Phthalein excretion was 5 per cent. in two hours.

Date	Time of Collection	Urine		Blood		Remarks
		Amount in C.c.	Uric Acid in Gm.	Uric Acid in Mg. per 100 C.c.	Nonprotein N in Mg. per 100 C.c.	
1915 June 26 July	.....	.....	....	3.5	68.6	Purin-free diet begun
1-2	7 a.m. - 7 p.m.	550	0.07			
2-3	.....	590	0.07			
3-4	.....	980	0.10			
4-5	.....	485	0.18			
5-6	.....	1,060	0.33			
6-7	.....	985	0.33			
7-8	.....	1,010	0.33			
8-9	.....	760	0.28			
9-10	.....	710	0.25			
10-11	.....	800	0.27			
11-12	.....	570	0.20			
12-13	.....	805	0.27			
13	1 p.m. 1 p.m. 5 p.m.	....	....	3.1 ..... 4.9	. .	0.5 gm. uric acid intravenously
13-14	7 a.m. - 7 a.m.	950	0.47			
14	11 a.m.	.....	....	4.1		
14-15	7 a.m. - 7 a.m.	935	0.35			
15	11 a.m.	.....	....	4.7		
15-16	7 a.m. - 7 a.m.	660	0.17			
16	11 a.m.	.....	....	2.9		
16-17	7 a.m. - 7 a.m.	923	0.35			
17-18	7 a.m. - 7 a.m.	904	0.34			

Endogenous output of uric acid July 5 to 13 = 2.36 gm.
Endogenous output of uric acid per day = 0.30 gm.
Exogenous output of uric acid July 14 to 15 = 0.22 gm.
Per cent. of injected uric acid excreted = 44 per cent.
Uric acid determinations were made by the original method.

CASE 7.—W. P. G., Med. No. 5471. Negro, male, aged 43.

Diagnosis: Gout; questionable chronic nephritis.

The patient's habits were good. During the last ten years he had had a dozen attacks of gout affecting the joints of the lower extremities and of the phalanges of the fingers. On physical examination numerous tophi were found in the ears and about the finger joints. Otherwise physical examination was negative. The blood pressure was 135 mm. systolic and 95 diastolic. The urine contained no casts, no blood and no epithelium. A scant trace of albumin was found once in the examination of several urine specimens. Phthalein excretion was 42 per cent. in two hours.

Date	Time of Collection	Urine		Blood		Remarks
		Amount in C.c.	Uric Acid in Gm.	Uric Acid in Mg. per 100 C.c.	Nonprotein N in Mg. per 100 C.c.	
1916 Oct. 21-22	7 a.m. - 7 a.m.	1,300	0.57	....	....	Purin-free diet begun
22-23	.....	1,165	0.52			
23	.....	.....	....	3.3	43.5	
23-24	.....	730	0.37			
24-25	.....	705	0.41			
25-26	.....	880	0.41			
26-27	.....	990	0.37			
27	7 a.m. - 10 a.m.	115	0.05			
	10 a.m. - 12 N.	90	0.08			
	12 N.	.....	....	4.1		
	12:15 p.m.	.....	....	.....	....	Intravenously 0.5 gm. uric acid
	12 - 2 p.m.	95	0.04			
	4 p.m.	.....	....	5.1		
	2 - 5 p.m.	180	0.07			
27-28	5 p.m. - 7 a.m.	430	0.21			
		910	0.44	.....	....	Total amount for 24 hours
28	4:15 p.m.	.....	....	4.3		
28-29	7 a.m. - 7 a.m.	905	0.41			
29-30	.....	625	0.28			
30-31	.....	840	0.39			
31-Nov. 1	.....	1,030	0.59			
1	.....	.....	....	.....	....	Mild attack of gout
1-2	.....	880	0.62	.....	....	Mild attack of gout
2-3	.....	1,350	0.59			
3-4	.....	1,080	0.51			
4-5	.....	1,035	0.58			
9	.....	.....	....	4.2	40.5	

Endogenous output of uric acid October 24 to 27 = 1.56 gm.
Endogenous output of uric acid per day = 0.39 gm.
Exogenous output of uric acid October 28 to 29 = 0.07 gm.
Per cent. of injected uric acid excreted = 14 per cent.
Uric acid determinations were made by the uric acid phenol reagent method.

CASE 8.—J. G., Med. No. 5421. White, male, aged 43.

Diagnosis: Gout; arteriosclerosis; hypertension; chronic myocarditis; very questionable chronic nephritis.

The patient had used beer freely. He had about sixteen attacks of severe polyarthritis of gouty character during the previous twenty-six years. Physical examination showed numerous tophi in the ears and on the fingers. The joints showed the changes of chronic arthritis. The radial artery walls were sclerosed. The blood pressure was 185 mm. systolic and 117 mm. diastolic. Otherwise physical examination was negative. The urine examinations were negative. Phthalein excretion was 52 per cent. in two hours.

Date	Time of Collection	Urine		Blood		Remarks
		Amount in C.c.	Uric Acid in Gm.	Uric Acid in Mg. per 100 C.c.	Nonprotein N in Mg. per 100 C.c.	
1916						
Oct. 10	.....	.....	....	6.4	....	Mixed diet
11	.....	.....	....	.....	....	Purin-free diet begun
13	.....	.....	....	.....	....	Acute attack of gout
15-16	7 a.m. - 7 a.m.	1,005	1.00	.....	....	Acute attack of gout
16-17	.....	960	1.01	.....	....	Acute attack of gout
17	.....	.....	....	5.4	....	Acute attack of gout
17-18	.....	1,260	0.71	.....	....	Acute attack of gout
18-19	.....	1,230	0.96	.....	....	Acute attack of gout
19-20	.....	Lost	....	.....	....	Acute attack of gout
20-21	.....	930	0.89	.....	....	Acute attack of gout
21-22	.....	905	0.68	.....	....	Acute attack of gout
22-23	.....	1,370	0.78	.....	....	Acute attack of gout
23-24	.....	1,355	0.80			
24-25	.....	870	0.44			
25-26	.....	830	0.70	.....	....	Attack subsided
26-27	.....	870	0.69			
27-28	.....	840	0.71			
28-29	.....	700	0.47			
29-30	.....	670	0.41			
30	12 N.	.....	....	4.1		
	12:15	.....	....	.....	....	0.5 gm. uric acid intravenously
	7 a.m. - 10 a.m.	105	0.08			
	10 a.m. - 12 N.	74	0.05			
	12 N. - 2 p.m.	171	0.11			
	2 - 5 p.m.	106	0.08	.....	....	
	4:15 p.m.	.....	....	4.6		
30-31	5 p.m. - 7 a.m.	330	0.22			
		786	0.52	.....	....	Total amount for 24 hours
31	12:15 p.m.	.....	....	4.8		
Oct. 31-Nov. 1	7 a.m. - 7 a.m.	820	0.51			
1-2	.....	930	0.49			
2-3	.....	950	0.63			
3-4	.....	750	0.61			
4-5	.....	670	0.46			
6	.....	.....	....	4.0	38.4	
Dec. 7	.....	.....	....	4.3	39.0	

The daily output of uric acid was too variable to permit an accurate determination of an average endogenous level.

Endogenous output of uric acid October 21 to 30 = 6.57 gm.

Endogenous output of uric acid per day = 0.66 gm.

Exogenous output of uric acid October 31 to November 5 = 0.

Uric acid determinations were made by the uric acid phenol reagent method.

CASE 9.—A. L. E., Med. No. 5297. White, male, aged 48.

Diagnosis: Gout; cirrhosis of the liver; questionable nephritis.

The patient had used large quantities of beer and whisky for many years. In the previous five years the patient had had five attacks resembling more the exacerbations of a chronic arthritis than gout. Three of these attacks occurred in the Peter Bent Brigham Hospital. Physical examination showed several tophi in the ears. The joints of the hands showed some periarticular thickening. The radial arteries were palpable. Blood pressure was 156 mm. systolic and 96 mm. diastolic. The liver edge was palpable 4 cm. below the right costal margin. Otherwise the physical examination was negative. The urine showed occasionally a scant trace of albumin and a few casts. Phthalein excretion was 24 per cent. in two hours.

Date	Time of Collection	Urine		Blood		Remarks
		Amount in C.c.	Uric Acid in Gm.	Uric Acid in Mg. per 100 C.c.	Nonprotein N in Mg. per 100 C.c.	
Oct. 14	.....	.....	....	.....	....	Purin-free diet begun
15	.....	.....	....	4.6	....	Acute gout
16-17	7 a.m. - 7 a.m.	850	0.94	.....	....	Acute gout
17-18	.....	750	0.93	.....	....	Acute gout
18-19	.....	550	0.55	.....	....	Acute gout
19-20	.....	Lost				
20-21	.....	500	0.48	.....	....	Mild acute gout
21-22	.....	490	0.44	.....	....	Mild acute gout
22-23	.....	630	0.51	.....	....	Mild acute gout
23-24	.....	430	0.23	.....	....	Mild acute gout
24-25	.....	870	0.56	.....	....	Mild acute gout
25-26	.....	785	0.62	.....	....	Mild acute gout
26-27	.....	1,040	0.54	.....	....	Mild acute gout
27-28	.....	1,100	0.76	.....	....	Mild acute gout
28-29	.....	720	0.58	.....	....	Mild acute gout
29-30	.....	786	0.49	.....	....	Mild acute gout
30-31	.....	525	0.35	.....	....	Mild acute gout
31-Nov. 1	.....	785	0.62	.....	....	Mild acute gout
1-2	.....	710	0.44			
2-3	.....	675	0.35			
3	7 a.m. - 10 a.m.	42	0.04			
	10 a.m. - 12 N.	67	0.05			
	12 N.	.....	....	3.5		
	12:15 p.m.	.....	....	.....	....	0.5 gm. uric acid intravenously
	12 N. - 2 p.m.	31	0.03			
	2 - 5 p.m.	87	0.06			
	4:15 p.m.	.....	....	5.7		
3-4	5 p.m. - 7 a.m.	219	0.18			
		416	0.37	.....	....	Total amount for 24 hours
4	.....	.....	....	5.1	32.6	
4-5	7 a.m. - 7 a.m.	218	0.20	.....	....	Questionable loss of one voiding of urine
5-6	.....	550	0.40			
6-7	.....	365	0.19			
7-8	.....	400	0.28			
8-9	....	480	0.32			
910	.....	460	0.29			
10-11	.....	485	0.29			
14	.....	.....	....	4.1		

The daily output of uric acid was too variable to permit an accurate determination of an average endogenous level.

Endogenous output of uric acid October 21 to November 3 = 6.42 gm.

Endogenous output of uric acid per day = 0.46 gm.

Exogenous output of uric acid November 4 to 11 = 0.

Uric acid determinations were made by the uric acid phenol reagent method.

A study of the foregoing protocols shows that in Case 6, of nephritis, 44 per cent. of the injected uric acid was excreted. It will be noted that from July 2 to 4 the daily excretion of uric acid in this case was less than 0.1 gm., while a few days later it had risen to more than 0.3 gm. Case 7, without evidences of nephritis, put out 14 per cent. of the uric acid injected. In Cases 8 and 9 the daily excretion of uric acid was too variable to permit the calculation of an average endogenous level with accuracy. There was, however, no apparent rise above the endogenous output after the intravenous injections. There is a question as to whether one voiding of urine was lost the second night following the uric acid injection in Case 9. The variability in the endogenous excretion of uric acid in these two cases, 8 and 9, is connected with the gouty attacks which occurred during the periods of observation. Comparable findings were obtained in another case of gout with tophi, not included here, in which we studied the uric acid excretion during an acute attack. A very mild gouty attack occurred the night of the sixth day following the injection of uric acid in Case 7. These findings confirm the observation of Brugsch and Schittenhelm[29] who reported that in the same cases of gout there were periods of low and periods of high endogenous uric acid excretion.

A study of the tables shows that the amounts of uric acid[30] found in the blood in different cases of gout while on a purin-free diet varied from 3.1 to 4.1 mg. per 100 c.c. Higher values than these were present in Cases 8 and 9 during acute attacks and at a time when the patient, Case 8, was receiving a mixed diet. An increase in the blood under these two conditions has been pointed out by one of us.[31] In all of the cases a rise of from 0.5 to 1.8 mg. of uric acid was present in the blood four hours after the intravenous injection of uric acid. This increase in blood uric acid persisted for forty-eight hours or longer in three of the cases (6, 8 and 9). In the remaining case (7) it disappeared within the first twenty-four hours. Three of these patients with gout retained the increase of uric acid in the blood twenty-four hours longer after the injection than did any of the nongouty patients.

Summary of the Results Obtained by the Intravenous Injections of Uric Acid.—Nine patients, five without gout and four with gout, have been given 0.5 gm. of uric acid intravenously. Determinations of the amounts of uric acid in the blood have shown a small but definite increase four hours after the injections in eight of the patients. From these findings it would seem highly probable that by the methods

29. Brugsch, T., and Schittenhelm, A.: Zur Stoffwechselpathologie der Gicht III Mittheilung. Ztschr. f. exper. Path. u. Therap., 1907, **4**, 480.

30. By uric acid in the blood we mean the substance determined by the colorimetric method of Folin and Denis.

31. Pratt, J. H.: Studies on the Uric Acid in the Blood in Gout. Am. Jour. Med. Sc., 1916, **151**, 92.

employed the substance quantitated in the blood after the intravenous injections was really uric acid. The increase in blood uric acid resulting after injection of uric acid disappeared within forty-eight hours after the injection in four nongouty and one of the gouty patients (Case 7). In the remaining three cases of gout it still persisted at the end of forty-eight hours.

The five nongouty patients excreted from 22 per cent. to 138 per cent. of the uric acid injected. Of the four cases of gout the one with nephritis put out 44 per cent. of the uric acid injected, while very little or none was excreted by the other three. These findings show that the failure to excrete a large percentage of uric acid after uric acid injections (exogenous uric acid) is not a pathognomonic symptom of gout, although it would seem to occur more frequently in gouty than in nongouty persons.

We have followed the method adopted by previous writers in computing the output of exogenous uric acid, to make our findings comparable with theirs. The method has been to determine the average daily endogenous uric acid excretion prior to the administration of purin-containing substances. After the injection or feeding of purin-containing materials all outputs in excess of the previously determined average endogenous output have been considered as exogenous uric acid.

This generally accepted method of calculation is often open to criticism. The daily outputs of endogenous uric acid are somewhat variable. It would probably be more correct to consider as exogenous uric acid only those outputs whose amounts are in excess of the maxi-

TABLE 4.—Results Obtained by the Two Methods of Calculating Exogenous Uric Acid Output

Case	Average Daily Endogenous Output of Uric Acid in Gm.	Exogenous Uric Acid Output		Maximum Daily Output of Endogenous Uric Acid in Gm.	Exogenous Output of Uric Acid Exceeding Maximum Daily Endogenous Output	
		Gm.	Per Cent.		Gm.	Per Cent.
1	0.54	0.41	32	0.61	0.20	40
2	0.69	0.69	138	0.78	0.42	84
3	0.30	0.32	64	0.36	0.20	40
4	0.31	0.11	22	0.34	0.08	16
5	0.56	0.29	58	0.63	0.15	30
6	0.30	0.22	44	0.28	0.09	18
7	0.39	0.07	14	0.41	0.03	6
8	0.66	0	0	0.89	0	0
9	0.46	0	0	0.78	0	0

mum endogenous output. Otherwise one cannot be sure that a certain amount of what is really endogenous uric acid has not been included in the portion computed as exogenous uric acid. We have calculated the exogenous output after the intravenous injections of uric acid in our cases on this basis and the results are given in Table 4. For purposes of comparison the exogenous outputs as determined by the generally accepted method are also given.

Considering as exogenous uric acid only those outputs which exceeded the maximum endogenous excretion gives lower figures for the percentages of uric acid excreted. By this method of calculation the anomalous exogenous excretion of 138 per cent. in Case 2 drops to the reasonable figure of 84 per cent. The excretion of 44 per cent. of exogenous uric acid by gout Case 6 becomes 18 per cent. by this method of calculation, which is a more reasonable amount in a case of gout with nephritis of severe type.

III. EXOGENOUS URIC ACID EXCRETION AFTER THE FEEDING OF PURIN OR NUCLEIN CONTAINING SUBSTANCES

We have studied the exogenous uric acid excretion after feeding sweetbreads to a patient with chronic arthritis and to two with gout. Previous observers have employed the results obtained by studies on the excretion of exogenous uric acid (1) as a basis for theories relating to the etiology of gout, and (2) as an aid in the diagnosis of that disease. It is generally accepted that gouty patients eliminate less exogenous uric acid than do normal persons. But whether or not this phenomenon is of diagnostic importance is not well established. Certainly there is much controversy regarding the rôle of uric acid in the etiology of gout.

For purposes of comparison we have tabulated from the literature figures for the output of exogenous uric acid derived from the feeding of purin or nuclein containing substances to normal persons, to patients with chronic arthritis, and to patients with gout. In all of the tables exogenous uric acid will be expressed as the percentage of purin nitrogen in the substances fed which was excreted as uric acid nitrogen. In making the tabulations figures given by the observers quoted have been subjected to certain changes. In expressing the amounts of uric acid and of purin nitrogen, numerals beyond the second decimal place have been dropped. No decimals have been used in expressing the percentages of purin nitrogen excreted as uric acid nitrogen. We have supplied calculations wherever those requisite for our purposes had not been made by the author. Our additional calculations are designated in the tables by an asterisk. Observations have been collected only in which the experimental subjects received a known amount of some purin or nuclein containing substance while on an otherwise purin-free diet. The findings for normal man are given in Table 5.

TABLE 5.—Summary of Previous Observations on Exogenous Uric Acid Excretion by Normal Man on a Purin-Free Diet

Observer	Observation Period	Daily Average Endogenous Output of Uric Acid in Gm.	Output of Exogenous Uric Acid in Gm.	Per Cent. of Purin Nitrogen Excreted as Uric Acid N	Number of Days of Exogenous Uric Acid Excretion	Substance Given	Purin Nitrogen in Substance Given†
Minkowski[32]....	1s	0.23	1.82*	49*	3*	3 gm. hypoxanthin in 1 day	1.24*
Krüger and Smith[33]	1	0.46	2.31	62	3	3 gm. hypoxanthin in 2 days	1.24
Ackroyd[34].....	1a	0.46	0.19	21	2	0.75 gm. hypoxanthin in 1 day	0.31
	1b	0.46	0.60	65	4	0.75 gm. hypoxanthin in 1 day	0.31
	2	0.42	0.66	72	2	0.75 gm. hypoxanthin in 1 day	0.31
	3	0.35	0.36	39	3	0.75 gm. hypoxanthin in 1 day	0.31
Brugsch and Schittenhelm[39]	10	0.24	1.28	23	2	Sodium thymonucleinate 30 gm. in 3 days	1.86
	12	0.36	1.54	24	1	Sodium nucleinate from yeast, 30 gm. in 3 days	2.17
Pollak[35].....	1	0.43	0.56	30	2	Sodium nucleinate 20 gm. in 1 day	0.79*
	2	0.42	0.45	28	2	10 gm. in 1 day	0.40*
	3	0.27	0.51	23	3	20 gm. in 1 day	0.79*
Mendel and Lyman[36]	W.W.H.	0.37	0.74	64	3	1.5 gm. hypoxanthin nitrate	0.39
	J.F.L.	0.38	0.66	57	3	1.5 gm. hypoxanthin nitrate	0.39
Plimmer, Dick, and Lieb[37]	..	0.43	0.12	..	1	13 gm. nucleic acid in 3 days	
Bloch[38].....	1	0.49	0.94	48	2	10 gm. nucleic acid in 1 day	0.68
	2	0.50	0.82	42	3	10 gm. nucleic acid in 1 day	0.66
	3	0.33	1.03	32	2	10 gm. nucleic acid in 1 day	0.66
Mallory[39].....	1	0.42	0.31	39	3	4 gm. nucleic acid in 1 day	0.26

* This figure represents our calculation made from the table given by the author quoted.
† The method of administration was per os in each instance.

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33. Krüger, M., and Schmid, J.: Die Entstehung der Harnsäure aus freien Purinbasen. Ztschr. f. Physiol. Chem., 1901-1902, **34,** 549.

34. Ackroyd, H.: Observations on Purin Metabolism. Bull. Com. for Study of Special Diseases, Edinburgh, 1907, **2,** 146.

35. Pollak, L.: Ueber Harnsäureausscheidung bei Gicht und Alkoholismus. Deutsch. Arch. f. klin. Med., 1907, **88,** 224.

36. Mendel, L. B., and Lyman, J. E.: A metabolism of Some Purin Compounds in the Rabbit, Dog, Pig, and Man. Jour. Biol. Chem., 1910-1911, **8,** 115.

37. Plimmer, R. H. A., Dick, M., and Lieb, C. C.: A Metabolism Experiment with Special Reference to the Origin of Uric Acid. Jour. Physiol., 1909-1910, **39,** 98.

38. Bloch, B.: Beiträge zur Kenntniss des Purinstoffwechsels beim Menschen. Deutsch. Arch. f. klin. Med., 1905, **83,** 499.

39. Mallory, W. J.: Observations on Uric Acid Excretion in Gout and Rheumatoid Arthritis. Bull. Com. for Study of Special Diseases, 1908-1909, **3,** 17.

TABLE 5.—Summary of Previous Observations on Exogenous Uric Acid Excretion by Normal Man on a Purin-Free Diet—(*Continued*)

Observer	Observation Period	Daily Average Endogenous Output of Uric Acid in Gm.	Output of Exogenous Uric Acid in Gm.	Per Cent. of Purin Nitrogen Excreted as Uric Acid N	Number of Days of Exogenous Uric Acid Excretion	Substance Given	Purin Nitrogen in Substance Given†
Morris[40].....	1	0.28	0.17	22	2	4 gm. nucleic acid in 1 day	0.26
Krüger and Smith[38]	1a	0.40	0.15	41	2	0.3 gm. adenin in 1 day	
	1b	0.46	0.31	41	3	0.6 gm. adenin in 1 day	
Hirschstein[41]...	4	0.36*	1.45*	11*	1	1,000 gm. thymus in 2 days	4.50*
Burian and Schur[42]	10	0.52	1.77	26	2	620 gm. thymus in 2 days	2.48
Ljungdahl[43]....	1	....	1.01	28	4	300 gm. thymus in 1 day	1.20
	2	....	1.37	36	5	300 gm. thymus in 1 day	1.20
	3	....	0.45	13	2	300 gm. thymus in 1 day	1.20
	4	....	0.87	24	2	300 gm. thymus in 1 day	1.20
	5	....	0.93	26	3	300 gm. thymus in 1 day	1.20
	6	....	1.17	33	3	300 gm. thymus in 1 day	1.20
Burian and Schur[42]	10	0.52	0.96	55	3	500 gm. liver in 1 day	0.6
	12	0.55	0.24	44	1	300 gm. ham in 1 day	0.18
	8	0.56	1.34*	74*	1	1,000 gm. beef in 4 days	0.6*
	5	0.29	0.52*	28*	1	760 gm. beef in 4 days	0.46*
Kaufmann and Mohr[44]	7	0.54*	2.71*	44*	2*	900 gm. veal in 4 days	0.54*
		0.54*	0.12*	8*	3*	900 gm. beef in 4 days	0.54*
	8	0.47*	0.58*	59*	2*	500 gm. beef in 3 days	0.30*
Plimmer, Dick and Lieb[37]	..	0.43*	2.77*	47*	3	3,500 gm. beef in 7 days	1.95*
Weiss[45].....	1	0.36	0.51	46	3	750 gm. beef in 2 days	0.38
		0.36	1.01	53	3	1,250 gm. beef in 2 days	0.63
Walker Hall[46]..	14	0.42	0.21	29	1	400 gm. beef in 1 day	0.24

40. Morris, E. H.: Observations on the Uric Acid Excretion in One Normal Person, and in Four Cases of Rheumatoid Arthritis. Bull. Com. for Study of Special Diseases, Edinburgh, 1910, **3**, 57.

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42. Burian, R., and Schur, H.: Ueber die Stellung der Purinkörper im menschlichen Stoffwechsel. Arch. f. d. gesamt. Physiol., 1900, **80**, 241.

43. Ljungdahl, M.: Ueber die Harnsäureausscheidung bei den chronischen nicht gichtischen Polyarthritiden und ihre Bedeutung fur die Differentialdiagnose zwischen Gelenkerkrankungen gichtischer und nicht gichtischer Natur. Ztschr. f. klin. Med., 1913-1914, **79**, 177.

44. Kaufmann, M., and Mohr, L.: Beitrage zur Alloxurkörperfrage und zur Pathologie der Gicht. Deutsch. Arch. f. klin. Med., 1902, **74**, 141 and 586.

45. Weiss, P.: Beiträge zur Wertbestimmung der Ausscheidung der endogenen und exogenen Harnsäure bei Gicht und anderen Erkrankungen. Ztschr. f. klin. Med., 1908, **66**, 131.

46. Hall, I. W.: The Purin Bodies of Foodsuffs. Manchester, 1902, p. 64.

Summary of Table 5. — In normal human beings after feeding hypoxanthin the percentage of purin nitrogen excreted as uric acid nitrogen varied from 21 per cent. to 72 per cent.; after feeding a nucleinate or nucleic acid, from 22 per cent. to 52 per cent.; after giving adenin it was 41 per cent.; after feeding thymus it varied from 11 per cent. to 38 per cent., and after beef, ham or veal, from 8 per cent. to 74 per cent. The mean average percentage of excretion of exogenous uric acid nitrogen after feeding the above named substances to normal individuals was 39 per cent., the extremes of excretion being 8 per cent. and 74 per cent. After feeding beef the exogenous uric acid varied from 8 per cent. to 44 per cent. in a person reported by Kaufmann and Mohr.[44] After administering hypoxanthin to a person reported by Ackroyd[34] the excretion of exogenous uric acid nitrogen was 21 per cent. after the first feeding and 65 per cent. after the second. Thus there is a considerable variation in the amount of exogenous uric acid both among different persons and in the same person.

The time required to complete the excretion of the exogenous uric acid varied from one to five days.

Table 6, showing the output of exogenous uric acid after feeding purin or nuclein containing substances to patients with chronic nongouty arthritis, is for the most part taken from one compiled by Mallory.[39] All patients were on a purin-free diet.

TABLE 6.—Summary of Previous Observations on Exogenous Uric Acid Excretion by Patients with Chronic Arthritis Who Were on a Purin-Free Diet

Observer	Observation Period	Daily Average Endogenous Output of Uric Acid in Gm.	Output of Exogenous Uric Acid in Gm.	Per Cent. of Purin Nitrogen Excreted as Uric Acid N	Number of Days of Exogenous Uric Acid Excretion	Substance Given	Purin Nitrogen in Substance Given†
Kaufmann and Mohr[44]	44	0.43	2.47	8	5	2,500 gm. thymus in 5 days	10
	45	0.47	2.33	13	3	1,500 gm. thymus in 3 days	6*
Ackroyd[34].....	4a	0.26	0.59	64	5	0.75 gm. hypoxanthin in 1 day	0.31
	4b	0.26	0.46	50	2	0.75 gm. hypoxanthin in 1 day	0.31
	5	0.33	0.44	49	3	0.75 gm. hypoxanthin in 1 day	0.31
	6	0.32	0.57	61	3	0.75 gm. hypoxanthin in 1 day	0.31
	7	0.35	0.40	43	2	0.75 gm. hypoxanthin in 1 day	0.31
	8	0.20	0.21	34	3	0.5 gm. hypoxanthin in 1 day	0.21
	9	0.22	0.92	99	6	0.75 gm. hypoxanthin in 1 day	0.31
	10	0.34	0.53	87	7	0.5 gm. hypoxanthin in 1 day	0.21
	11	0.58	0.61	100	7	0.5 gm. hypoxanthin in 1 day	0.21
	12	0.49	0.31	33	6	0.75 gm. hypoxanthin in 1 day	0.31
	14	0.34	0.41	44	9	0.75 gm. hypoxanthin in 1 day	0.31

* This figure represents our calculation made from the table given by the author quoted.
† The method of administration was per os in each instance.

TABLE 6.—Summary of Previous Observations on Exogenous Uric Acid Excretion by Patients with Chronic Arthritis Who Were on a Purin-Free Diet—(*Continued*)

Observer	Observation Period	Daily Average Endogenous Output of Uric Acid in Gm.	Output of Exogenous Uric Acid in Gm.	Per Cent. of Purin Nitrogen Excreted as Uric Acid N	Number of Days of Exogenous Uric Acid Excretion	Substance Given	Purin Nitrogen in Substance Given†
Mallory[39].....	1b	0.35	0.14	15	2	0.75 gm. hypoxanthin in 1 day	0.31
	2b	0.30	0.24	25	4	0.75 gm. hypoxanthin in 1 day	0.31
	c	0.30	0.33	35	3	0.75 gm. hypoxanthin in 1 day	0.31
	d	0.30	0.25	27	3	0.75 gm. hypoxanthin in 1 day	0.31
	3b	0.30	0.50	53	2	0.75 gm. hypoxanthin in 1 day	0.31
	5b	0.30	0.55	59	4	0.75 gm. hypoxanthin in 1 day	0.31
	6b	0.31	0.38	41	3	0.75 gm. hypoxanthin in 1 day	0.31
Morris[40].....	2b	0.21	0.25	27	3	0.75 gm. hypoxanthin in 1 day	0.31
	3b	0.20	0.40	43	3	0.75 gm. hypoxanthin in 1 day	0.31
Mallory[39].....	1a	0.35	0.06	7	3	4 gm. nucleic acid in 1 day	0.26
	2a	0.30	0.24	31	2	4 gm. nucleic acid in 1 day	0.26
	3a	0.30	0.26	32	2	4 gm. nucleic acid in 1 day	0.26
	4	0.39	0.36	46	3	4 gm. nucleic acid in 1 day	0.26
	5a	0.30	0.63	80	8	4 gm. nucleic acid in 1 day	0.26
	6a	0.31	0.76	97	6	4 gm. nucleic acid in 1 day	0.26
Morris[40].....	2a	0.21	0.14	18	4	4 gm. nucleic acid in 1 day	0.26
	3a	0.20	0.14	18	3	4 gm. nucleic acid in 1 day	0.26
	4	0.31	0.81	103	7	4 gm. nucleic acid in 1 day	0.26
Ljungdahl[43]....	1	....	0.95	26	2	300 gm. thymus	1.20
	2	....	0.54	15	2	300 gm. thymus	1.20
	3	....	0.39	11	2	300 gm. thymus	1.20
	4	....	0.46	19	2	200 gm. thymus	0.80
	5	....	0.69	19	2	300 gm. thymus	1.20
	6	....	1.15	48	7	200 gm. thymus	0.80
	7	....	1.20	33	7	300 gm. thymus	1.20
	8	....	0.50	14	2	300 gm. thymus	1.20
	9	....	0.95	26	5	300 gm. thymus	1.20
	10	....	0.28	8	1	300 gm. thymus	1.20
	11	....	0.24	7	1	300 gm. thymus	1.20
	12	....	1.12	31	6	300 gm. thymus	
Hösslin and Kato[47]	1	0.28*	1.41*	60*	5*	10 gm. sodium nucleinate	0.66*
	4	0.30*	0.12*	6*	2*	10 gm. sodium nucleinate	0.66*
	5	0.35*	2.30*	80*	5*	15 gm. sodium nucleinate	0.99*
	6	0.32*	0.70*	24*	3*	15 gm. sodium nucleinate	0.99*
	8	0.35*	0.14*	7*	1*	10 gm. sodium nucleinate	0.99*
	10	0.29*	0.20*	6*	1*	15 gm. sodium nucleinate	0.99*
	11	0.34*	0.02*	1*	1*	15 gm. sodium nucleinate	0.99*
	12	0.42*	0.50*	31*	4*	15 gm. sodium nucleinate	0.99*

47. von Hösslin, H., and Kato, K.: Ueber Harnsäureausscheidung bei Gicht und Gelenkrheumatismus. Deutsch. Arch. f. klin. Med., 1910, **99,** 301.

Summary of Table 6.—In patients with chronic nongouty arthritis the percentage of purin nitrogen excreted as uric acid nitrogen after feeding hypoxanthin ranged from 15 per cent. to 99 per cent., after giving nucleic acid from 77 per cent. to 103 per cent., after sodium nucleinate from 1 per cent. to 80 per cent., and after thymus from 8 per cent. to 48 per cent. The mean average excretion of all these substances was 38 per cent. After feeding hypoxanthin the exogenous uric acid excretion varied from 50 per cent. to 64 per cent. in one of Ackroyd's[34] cases, and from 25 per cent. to 35 per cent. in one reported by Mallory.[39] The table shows that there is great variation in the amount of exogenous uric acid excreted by the different patients. This was also found in normal persons (Table 5). The time required to excrete the exogenous uric acid varied from one to nine days.

The cases reported by Kaufmann and Mohr,[44] Ackroyd,[34] Mallory[39] and Morris[40] were without evidences of nephritis. It is inferred from the text in the reports of Ljungdahl[43] and of Hösslin and Kato[47] that the patients were not nephritics.

We have studied the excretion of uric acid after a meal of sweetbreads in a patient with chronic polyarthritis. There were no evidences of kidney disease or of gout in this patient. The findings are given in Table 7.

TABLE 7.—Exogenous Uric Acid Excretion in Chronic Arthritis

(W. H. K. Med. No. 5278. Diagnosis: Chronic arthritis. For notes on this patient see Case 5.)

Date	Time of Collection	Urine		Blood		Remarks
		Amount in C.c.	Uric Acid in Gm.	Nonprotein N in Mg. per 100 C.c.	Uric Acid in Mg. per 100 C.c.	
Oct. 31	.....	.....	....	.....	....	Purin-free diet begun
Nov. 9.	.....	.....	....	27.9	1.5	
16-17	7 a.m. - 7 a.m.	1,480	0.44			
17-18	.....	1,010	0.29			
18-19	.....	845	0.38			
19-20	.....	1,225	0.37			
20-21	.....	1,310	0.43			
21	1 p.m.	.....	....	.....	....	Patient given 184 gm. sweetbreads
	7 p.m.	.....	....	.....	2.6	
21-22	1 p.m. - 1 p.m.	7,429	0.93			
22	11 a.m.	.....	....	.....	1.5	
22-23	1 p.m. - 1 p.m.	1,490	0.53			
23-24	1 p.m. - 1 p.m.	925	0.49			
24-25	1 p.m. - 1 p.m.	905	0.33			

Endogenous output of uric acid November 17 to 21 = 2.01 gm.
Endogenous output of uric acid per day = 0.40 gm.
Exogenous output of uric acid November 22 to 24 = 0.75 gm.
Purin nitrogen in 184 gm. of sweetbreads calculated according to Burian and Schur = 0.83 gm.
Per cent. of purin nitrogen excreted = 30 per cent.
Uric acid determinations made by the uric acid reagent method.

Thirty per cent. of the purin nitrogen fed was excreted as uric acid nitrogen by our patient. These findings are comparable to those reported in the literature.

The exogenous uric acid excretion by gouty persons who were under the same experimental conditions as the normal and arthritic subjects in the foregoing tables is given in Table 8.

TABLE 8.—SUMMARY OF PREVIOUS OBSERVATIONS ON EXOGENOUS URIC ACID EXCRETION BY GOUTY PERSONS ON A PURIN-FREE DIET

Observer	Observation Period	Daily Average Endogenous Output of Uric Acid in Gm.	Output of Exogenous Uric Acid in Gm.	Per Cent. of Purin Nitrogen Excreted as Uric Acid N	Number of Days of Exogenous Uric Acid Excretion	Substance Given	Purin Nitrogen in Substance Given†
Brugsch and Schittenhelm[49]	4	0.73	0.29	14	4	Sodium thymonucleinate, 20 gm. in 2 days	1.24
	5	0.33	0.57	15	5	Sodium thymonucleinate, 20 gm. in 2 days	1.24
	11	0.13	0.35	6	6	Sodium thymonucleinate, 30 gm. in 3 days	1.86
See Footnote 49	8	0.25	0.16	16	3	Sodium thymonucleinate, 5 gm. in 1 day	0.31
See Footnote 29	4	0.22	0.44	20	4	Yeast sodium nucleinate, 10 gm. in 1 day	0.72
		0.22	0.44	20	4	Yeast sodium nucleinate, 50 gm. in 5 days	3.61
	5	....	0.00	0	0	Yeast sodium nucleinate, 20 gm. in 2 days	1.44
	13	0.31	1.54	26	5	Yeast sodium nucleinate, 20 gm. in 2 days	1.44
Neustadt[48].....	K2	0.48	0.09	0	..	8 gm. thymonucleic acid in 1 day	
Pollak[28].....	4	0.06	0.19	16	4	10 gm. nucleic acid in 1 day	0.40
	5	0.23	0.24	19	2	10 gm. nucleic acid in 1 day	0.40
	6	0.27	0.43	20	3	18 gm. nucleic acid in 1 day	0.71
Mallory[29].....	9a	0.18	0.02	3	1	4 gm. nucleic acid in 1 day	0.26
	10a	0.21	0.02	3	1	4 gm. nucleic acid in 1 day	0.26
	11a	0.17	0.24	30	4	4 gm. nucleic acid in 1 day	0.26
Brugsch and Schittenhelm[49]	1	0.29	0.16	13	2	1 gm. hypoxanthin in 1 day	0.41
	2	0.29	0.15	12	1	1 gm. hypoxanthin in 1 day	0.41
Mallory[29].....	9b	0.18	0.03	3	1	0.75 gm. hypoxanthin in 1 day	0.31
	10b	0.21	0.09	10	2	0.75 gm. hypoxanthin in 1 day	0.31
	11b	0.17	0.10	10	3	0.75 gm. hypoxanthin in 1 day	0.31

* This figure represents our calculation made from the table given by the author quoted.
† The method of administration was per os in each instance.

48. Neustadt, G.: Das Verhalten verfütterter Purinbasen bei der Gicht. Ztschr. f. exper. Path. u. Therap., 1911-1912, **10,** 296.

49. Brugsch, T., and Schittenhelm, A.: Zur Stoffwechselpathologie der Gicht. VIII Mittheil. Ztschr. f. exper. Path. u. Therap., 1908-1909, **5,** 215.

TABLE 8.—Summary of Previous Observations on Exogenous Uric Acid Excretion by Gouty Persons on a Purin-Free Diet—(*Continued*)

Observer	Observation Period	Daily Average Endogenous Output of Uric Acid in Gm.	Output of Exogenous Uric Acid in Gm.	Per Cent. of Purin Nitrogen Excreted as Uric Acid N	Number of Days of Exogenous Uric Acid Excretion	Substance Given	Purin Nitrogen in Substance Given†
Rotky[50].....	3-2	0.34	0.07	11	3	0.5 gm. hypoxanthin in 1 day	0.21
Neustadt[49].....	1-2	0.36	0.79	109	4	0.5 gm. hypoxanthin in 1 day	0.21
	K2	0.48	0.02	5	3	0.25 gm. hypoxanthin in 1 day	0.10
		0.45	0.38	61	3	0.5 gm. hypoxanthin in 1 day	0.21
		0.48	0.09	15	3	0.5 gm. hypoxanthin in 1 day	0.21
		0.51	0.42	60	4	0.5 gm. hypoxanthin in 1 day	0.21
Levine and Kristeller[51]	1	0.24	0.15	20	4	7.5 gm. uric acid in 1 day	2.5
		0.24	0.00	0	0	7.5 gm. uric acid in 1 day	2.5
	2	0.23	1.14	5	6	24 gm. uric acid in 4 days	8.0
		0.23	0.86	2	2	24 gm. uric acid in 4 days	8.0
	1	0.23	0.23	3	4	Nucleic acid, 1 day	2.83
	2	0.23	1.10	6	4	Nucleic acid, 4 days	8.0
Neustadt[48].....	1-6	0.41	0.21	28	3	0.35 gm. adenin in 1 day	0.18
Brugsch and Schittenhelm[49]	..	0.25	0.44	41	5	0.7 gm. adenin in 1 day	0.36
Kaufmann and Mohr[44]	39	0.46*	2.31*	22*	4*	800 gm. thymus in 4 days	3.60*
	40	0.50*	1.44*	12*	2*	900 gm. thymus in 2 days	4.05*
	41	0.49*	1.30*	8*	2*	1,200 gm. thymus in 4 days	5.40*
	42	0.40*	0.72*	5*	1*	900 gm. thymus in 3 days	4.05*
	46	0.32*	2.69*	22*	5+*	900 gm. thymus in 3 days	4.05*
Strauss[52].....	..	0.41*	0.33*	8*	2	325 gm. thymus in 1 day	1.46*
Brugsch[53].....	1	0.55*	0.00*	0.00*	0*	800 gm. thymus in 4 days	3.00*
Hirschstein[41]...	5	0.06*	17*	9*	0+*	1,000 gm. thymus in 2 days	4.50*
Rotky[54].....	3	0.34*	0.04	3	2	100 gm. thymus in 1 day	0.45*
Kaufmann and Mohr[44]	47	0.39	0.40	27*	1	800 gm. veal in 4 days	0.48*
		0.40	0.20	21*	1	800 gm. beef in 4 days	0.48*
Soetbeer[54].....	3	0.42	0.12	25*	1+*	250 gm. beef in 1 day	0.15*
	4	0.50	0.08	10*	2+*	500 gm. beef in 1 day	0.30*
	5	0.50*	0.00*	0.00*	..	700 gm. beef in 2 days	0.15*
Brugsch[53].....	..	0.55	0.09	0.00	..	800 gm. beef in 3 days	0.48*
Soetbeer[54].....	2	0.28	0.92	57	3+*	900 gm. ham in 3 days	0.54*
Weiss[45].....	..	0.29	0.42	27	8	750 gm. beef	0.58
Hall[55].....	4	0.17*	0.22*	100	3	Beef extract	0.07

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Summary of Table 8.—In gouty patients the percentage of purin base nitrogen excreted as uric acid nitrogen after feeding hypoxanthin varied from 5 per cent. to 109 per cent., after adenin it was 40 per cent., after giving nucleic acid it ranged from 3 per cent. to 30 per cent., after sodium nucleinate from none to 36 per cent., after thymus from none to 22 per cent., and after some form of beef or ham from none to 106 per cent. The mean average percentage of excretion as exogenous acid nitrogen of all these substances fed was 20 per cent.

It will be noted that the exogenous uric acid output in the patients whose urine contained albumin and casts was as great as in those in whom the urine was reported as normal.

We have studied the uric acid excretion in two cases of gout after feeding sweetbreads. The findings are given in Tables 9 and 10. The patient whose data are given in Table 8 has already been described as Case 9. The patient whose data appears in Table 9 was one who used alcoholic drinks to excess. During the previous nine years the patient had had six attacks of podogra in the right great toe joint. In the previous six years there had been several polyarticular attacks of arthritis, gouty in nature, which involved the joints of the hands, knees, toes and ankles. During the study of the patient's uric acid excretion an attack of gout occurred the day following the ingestion of 188 gm. of sweetbreads. The middle finger, dorsum of the hand and wrist were involved. On physical examination large tophi were found in the left ear, about the olecranan processes of both ulnae and on the plantar surfaces of both wrists, and on all the fingers. Sodium urate crystals were obtained from certain of the tophi. There were no evidences of cardiovascular disease. The blood pressure was 126 mm. systolic and 96 mm. diastolic. The urine contained neither albumin nor casts. The patient was put on a purin-free diet Oct. 8, 1916.

TABLE 9.—Exogenous Uric Acid Excretion in Gout

(A. L. E., Med. No. 5297. Diagnosis: Gout.)

Date	Time of Collection	Urine		Blood		Remarks
		Amount in C.c.	Uric Acid in Gm.	Nonprotein N in Mg. per 100 C.c.	Uric Acid in Mg. per 100 C.c.	
1916 Nov. 1	.....	.....	....	.....	....	Purin-free diet begun
20-21	7 a.m. - 7 a.m.	475	0.15			
21-22	.....	Lost				
22-23	7 a.m. - 7 a.m.	695	0.14			
23-24	7 a.m. - 7 a.m.	460	0.10			
24-25	7 a.m. - 7 a.m.	715	0.13			
25	1 p.m.	.....	....	54.3	4.5	
	1 p.m.	.....	....	.....	....	Patient given 150 gm. sweetbreads
	7 p.m.	.....	....	.....	5.3	
25-26	1 p.m. - 1 p.m.	725	0.19			
26	1 p.m.	.....	....	.....	5.1	
26-27	1 p.m. - 1 p.m.	805	0.19			
27-28	1 p.m. - 1 p.m.	735	0.18			
29	1 p.m.	.....	....	.....	4.8	

Endogenous output of uric acid November 21 to 25 = 0.52 gm.
Endogenous output of uric acid per day = 0.13 gm.
Exogenous output of uric acid November 26 to 27 = 0.12 gm.
Purin nitrogen in 150 gm. of sweetbreads calculated according to Burian and Schur = 0.68 gm.
Per cent. of exogenous purin nitrogen excreted = 6.
Uric acid determinations made by the uric acid reagent method.

TABLE 10.—Exogenous Uric Acid Excretion in Gout After Feeding Sweetbreads

J. J. N. White, male, aged 35. Many tophi on hands and feet. Diagnosis: Gout.

Date	Time of Collection	Urine		Blood, Uric Acid in Mg. per 100 C.c.	Remarks
		Amount in C.c.	Uric Acid in Gm		
1916 Oct. 7	.....	.....	....	...	Purin-free diet begun
12-13	7 a.m. - 7 a.m.	1,690	0.26		
13-14	7 a.m. - 7 a.m.	1,440	0.25		
14-15	7 a.m. - 7 a.m.	1,570	0.27		
15-16	7 a.m. - 7 a.m.	1,860	0.26		
16-17	7 a.m. - 7 a.m.	2,100	0.33		
17-18	7 a.m. - 7 a.m.	1,860	0.25		
18-19	7 a.m. - 7 a.m.	1,770	0.25		
19-20	7 a.m. - 7 a.m.	1,515	0.40		
20	12 noon	.....	....	2.2	188 gm. of thymus
20-21	7 a.m. - 7 a.m.	1,620	0.49	4.4	Acute attack of gout
21-22	7 a.m. - 7 a.m.	2,100	0.59	8.7	
22-23	7 a.m. - 7 a.m.	1,500	0.29	2.7	
23-24	7 a.m. - 7 a.m.	1,995	0.37		
24-25	7 a.m. - 7 a.m.	1,660	0.25	5.0	
Nov. 7	.....	.....	....	7.4	

Endogenous output of uric acid October 13 to 19 = 1.87 gm.
Endogenous output of uric acid per day = 0.27 gm.
Exogenous uric acid excreted October 21 to 22 = 0.67 gm.
Purin nitrogen in 188 gm. of sweetbreads according to Burian and Schur = 0.9 gm.
Percentage of purin nitrogen excreted as uric acid nitrogen = 24.

Our patients with gout excreted 6 per cent. and 24 per cent. of the purin nitrogen contained in the sweetbreads in the form of uric acid nitrogen. These findings are comparable to those reported for gout cases in the literature.

The results obtained by a comparative study of exogenous uric acid excretion by normal, by arthritic, and by gouty persons are shown in Tables 11 and 12.

TABLE 11.—Percentage of Purin Nitrogen Excreted as Uric Acid Nitrogen After Feeding Purin or Nuclein Containing Substances

Diagnosis	Number of Cases	Total Number of Experiments	Number of Experiments and Percentages of Purin Nitrogen Excreted as Uric Acid Nitrogen			
			0-10	10-20	20-30	30-100
Normal	35	40	1	2	11	26
Chronic arthritis	41	32	8	9	7	28
Gout	22	50	19	13	7	11

Table 11 shows conclusively that the output of exogenous uric acid is usually smaller in gout than in either normal or arthritic persons.

Twenty-eight, or 87.9 per cent., of the gouty patients excreted as uric acid nitrogen less than 20 per cent. of the purin nitrogen ingested, while thirty-one, or 88.6 per cent., of normal persons and twenty-five, or 69.7 per cent., of nongouty, arthritic patients excreted more than 20 per cent. Regardless of the substances fed the average exogenous uric acid nitrogen excretion in gout was 20 per cent., while by the normal persons it was 39 per cent., and by arthritic patients 38 per cent. The small output of exogenous uric acid occurs frequently enough in gout to be considered as a symptom of that disease. But as a pathognomonic symptom of gout it is not of much importance, since it also occurs in 11.4 per cent. of normal persons, and in 30.3 per cent. of arthritic nongouty patients.

A prolonged excretion of exogenous uric acid has been considered as a symptom of gout. The duration in days of the output of exogenous uric acid has been compiled from Tables 5 to 10 and the results are given in Table 12.

TABLE 12.—Duration in Days of Exogenous Uric Acid Excretion After Feeding Purin or Nuclein Containing Substances

Diagnosis	Number of Cases	Total Number of Experiments	Number of Experiments with Duration in Days of Exogenous Uric Acid Excretion								
			1	2	3	4	5	6	7	8	9
Normal	35	40	6	15	16	2	1				
Chronic arthritis	41	52	5	13	15	4	4	4	5	1	1
Gout	32	46	9	10	11	7	4	2	1	2	

All normal persons excreted the exogenous uric acid within five days. Of fifty-two experiments on arthritic patients, the exogenous uric acid output was completed within five days in forty-one, or 78.8 per cent., and of forty-six experiments on the gouty persons the output was completed within five days in forty-one, or 89.1 per cent. Therefore, a prolongation of the excretion of exogenous uric acid over that of the normal does not occur frequently enough in gout to be considered a symptom of that disease.

The striking fact brought out in the last two tables is the great variations in the percentage output of exogenous uric acid and in its duration. Either a delayed and diminished output is not evidence of disturbances in the intermediary metabolism of nucleins, or the intermediary metabolism of nucleins is easily deranged.

SUMMARY AND DISCUSSION

Our studies on the intravenous injection of uric acid and the feeding of nuclein containing material, together with the compilations we have made from reports in the literature, show that in normal and non-gouty as well as in gouty persons there is great variability in the quantity and in the duration of exogenous uric acid excretion. For this reason a diminished or a protracted exogenous uric acid output most probably results from factors other than disturbances in the nuclein intermediary metabolism. If this is not true, then derangements in nuclein metabolism are so common that their importance in the etiology of any diseased condition is problematic.

Umber[56] advanced the hypothesis that the failure of gouty persons to excrete exogenous uric acid was due to a special affinity of the tissues for uric acid. We have found that intravenously injected uric acid usually remains in the blood stream longer in gouty than in non-gouty persons. The reverse would have been expected if Umber's theory were correct.

By statistical evidence we have shown that in the majority of gouty persons the uric acid in the blood is more than 3 mg. per 100 c.c. when determined by the method of Folin and Denis. That the substance which has been determined was actually uric acid is made probable by the following considerations: (1) It is well known that in gout there is a deficient output of uric acid; this substance would then tend to accumulate in the blood; (2) less uric acid is found in the blood of persons without gout than of those with that disease. The conditions which form exceptions to this statement have already been enumerated, but their character is such that in the large majority retention of uric acid is readily explained; (3) following the intravenous injections of uric acid an increase in that substance occurs in the blood.

The fate of that part of intravenously injected uric acid which is not excreted within the first few days is unknown. In fact, this additional uric acid disappeared from the blood in all of our cases, except one, before its excretion began. Since uric acid is not known to be destroyed in the body, we offer the explanation that the excess which we injected went into the body tissues. Van Slyke[57] has shown that intravenously introduced amino-acids quickly disappear from the blood. He discovered that they were to be found in the muscles, where they were held either mechanically or in loose molecular combinations.

56. Umber, F.: Ernährung und Stoffwechselkrankheiten. Ed. 2, Berlin, 1914.

57. Van Slyke, D. D.: The Fate of Protein Digestion Products in the Body. III. The Absorption of Amino-Acids from the Blood and Tissues. Jour. Biol. Chem., 1914, **16**, 197.

Urea[58] behaves in the same manner. That the intravenously injected uric acid does not enter into some combinations in the blood which prevents its determination by the Folin and Denis method is indicated by the ability to recover all uric acid which is added to blood in vitro.

From our studies and those of others it appears that more than 3 mg. per 100 c.c. of blood is a symptom of gout. But whether or not retention of uric acid after its intravenous injection, or after feeding substances containing purin or nucleins, is to be regarded as evidence of gout is open to question, since we have shown that the failure to eliminate exogenous uric acid is not peculiar to gout.

We are impressed with the importance of carrying out studies on uric acid elimination on persons who are really normal. It may be doubted whether some of the so-called normal subjects used for physiologic studies on uric acid elimination were not pathologic. Before considering an experimental subject as normal it is necessary that a thorough medical examination be made and that the modern laboratory tests, especially those for renal function, be employed.

CONCLUSIONS

1. More than 3 mg. of uric acid per 100 c.c. of blood, with the patient on a purin-free diet, is a symptom of gout, but it is not diagnostic of this disease.

2. No relation exists between the amount of uric acid and of total nonprotein nitrogen found in the blood of gouty persons.

3. A marked retention of nonprotein nitrogen is not frequent in gout.

4. The excretion of exogenous uric acid by normal, by arthritic, and by gouty persons varies greatly both in amount and in duration.

5. The retention of exogenous uric acid is a symptom of questionable importance in the diagnosis of gout.

We wish to thank Dr. Christian for allowing us to study the gouty patients in his wards. We are much indebted to Dr. Otto Folin for advice in the interpretation of certain findings. The three cases of insanity were studied at the Boston Psychopathic Hospital through the courtesy of Dr. E. E. Southard. One of the cases of gout was studied at the Massachusetts General Hospital through the cooperation of the orthopedic department.

58. Marshall and Davis: Urea: Its Distribution and Elimination from the Body. Jour. Biol. Chem., 1914, **18**, 53.

THE FERMENT-ANTIFERMENT BALANCE AND ITS RELATION TO THERAPEUSIS *

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For many years able and patient investigators have been occupied with the elaboration of the science of immunology. Numerous have been the achievements that have rewarded the direction of the foremost medical workers into these channels of thought and research; indeed, so splendid and satisfying have been many of them that we have gradually come to assume that therapeutic advance can take place only along these well demarcated lines. And yet, certain of the commoner infections have failed to yield to the intricate structure that has been reared in the effort to overcome them; failure which we have felt was due not to the method of attack, but to present limitations in the application of the theory by individual investigators. The study of tuberculosis illustrates the point most clearly. The end-result of innumerable immunologic studies has here left the problem of therapeusis practically unaltered; tuberculin therapy, introduced on a background of strictly immunologic research, while still offering the most favorable therapeutic result in selected cases, is no longer to be considered an immunizing agent in the specific sense of the term; the present time finds the laboratories devoted to tuberculosis research turning largely to studies along chemotherapeutic lines. It would seem justifiable, therefore, to explore the possibility of new avenues of approach to therapeutic problems; to determine whether or not some other broad basis can be found that, with proper study, will lead to fruitful therapeutic results. With this idea in mind the following outline is presented, not to be accepted as a completed study, but merely to offer briefly the rudiments of the problems when examined from a nonimmunologic standpoint.

The fundamental factor in overcoming bacterial intoxication not due to the soluble exotoxins lies in the ability of the cells or fluids of the invaded organism to digest the toxic protein fragments to their lowest degradation products and in this way overcome their deleterious effect. Digestion, too, no matter under what immunologic term we wish to classify the particular phase, must be considered the basis of the phenomena which have to do with overcoming bacterial invasion

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itself. Might it not be warranted, therefore, to study in greater detail these digestive forces and their relation to pathologic conditions, in the hope of eventually being able to control ferment activity and achieve therapeutic results thereby?

To Abderhalden and his school in Germany we owe the beginning of such a movement; unfortunately, the center of interest was nearly shifted from a study of fundamental phenomena to particularistic and technical details involved in the clinical popularization of the so-called Abderhalden test for pregnancy. Abderhalden was undoubtedly prejudiced in favor of the idea of the specificity of proteolytic ferments because of the beautiful specificity displayed by the ferments that hydrolize the carbohydrates. When, however, one considers that the variety of carbohydrates with which ferments have to deal is relatively limited as contrasted with the practically endless combinations possible in the protein molecule, this prejudice is not necessarily logical. Possibly Abderhalden was influenced, too, by the immunologic conception of specificity; indeed, did hope to answer just this problem on the basis of highly specific proteases. The final demonstration that the Abderhalden reaction for pregnancy had not the merit of specificity emphasized by Abderhalden, unfortunately had a tendency to check further investigation in this field. Jobling was the first in this country to recognize the importance of, and to systematically study, ferment action in relation to pathologic conditions, and began his work some time previous to the investigations of Abderhalden in this particular line. In a series of some thirty odd articles,[1] a broad experimental foundation has been laid on which it seems possible to attempt clinical investigation along lines not previously considered. In order to correlate the ideas which underlie the following studies it may be advisable to discuss briefly in this article some of the phenomena which Jobling has studied.

Vaughn, Matthes and Krehl, Friedberger and numerous other investigators have established the relation between intoxication and fever and the causal relation of the protein split products thereto. We are therefore justified in assuming that with bacterial invasion the intoxication of the organism is due to bacterial proteins; there is also a possibility that the proteins of the host themselves may, under certain conditions, give rise to toxic split products; the source, however, need not for the moment concern us.

If we are justified in ascribing major importance to these protein derivatives, we are equally justified in studying the mechanism of detoxication, which must involve the proteolytic ferments that will break down the toxic complexes to nontoxic forms. Several proteolytic ferments may occur in the serum. (1) The leucoproteases: (*a*)

1. Jour. Exper. Med., 1912-1916, **16-23.**

an alkaline active ferment capable of splitting native protein largely to the proteose stage; (*b*) an acid active ferment with a similar range of activity; (*c*) an ereptase, active in both acid and alkaline reaction and splitting partially hydrolyzed proteins to the amino-acid stage. These ferments are derived from disintegrating but not from living leukocytes, and the fluctuations in the leukocyte count have therefore no direct bearing on the amount of these ferments in the serum. Of the ferments of this possible derivation only the ereptase is able to act in the presence of blood serum and tissue fluids, because the true proteases are inhibited by the antiferment. In a localized area, however, the amount of such ferments liberated may be sufficient to saturate the antiferment, and in this case digestion can go the entire stage from native protein to amino-acid. (2) Serum protease: a polyvalent, trypsin-like ferment, active in neutral, or even in slightly acid or alkaline reactions, is completely inhibited by the antiferment. It becomes active in the body only when the antiferment is removed or diminished, and is able to digest any native protein to the amino-acid stage. It is present in small amounts in normal human serum, but in relatively large amounts in certain of the lower animals. (3) Serum peptidase: a polyvalent ferment active in the presence of the serum antiferment, able to digest partly hydrolyzed proteins to the amino-acid stage and active in reactions similar to those favorable for protease action. It is present in normal human serum in small amounts.

These ferments should not be confused with the alexin, or complement, which is slightly less resistant to heat and is destroyed by the lipoid solvents. Whether or not these ferments always act in a lytic capacity, or may under certain conditions become synthetic, is a question as yet unsettled.

Inasmuch as the first two types of ferment are active only under special conditions and are not present in more than small amounts in the serum at any time, they are of relatively less import than the last ferment, the peptidase. It is at once apparent that we are dealing here with the detoxicating agent, a ferment that hydrolyzes proteins from the toxic stages — albumoses (proteoses) and peptones — to the nontoxic amino-acids. A mobilization of this ferment could then be considered only as of beneficial significance, never as a factor in the production of an intoxication, and, since it is active in the presence of the antiferment, the fluctuations of the latter in titer would have no effect on the detoxicating force. An increase in the amount of this ferment occurring spontaneously during the course of disease should, therefore, be coincident with clinical improvement and, conversely, the disappearance of the ferment should permit the accumulation of toxic split products and an increase in intoxication. An increase induced arti-

ficially, if possible, should be equally effective as a measure of detoxication.

When we turn to the true proteases we deal with a reaction of which the possibilities are more complex for two principal reasons: (*a*) the ferment action may involve the splitting of native proteins to the higher split products and may conceivably, at some time in the process, give rise to intoxication; (*b*) the ferment action is balanced by the presence of the antiferment, and we have therefore to deal with two variable factors. For simplicity we may take two concrete examples. Suppose that a pneumonic focus with its mass of cellular detritus and fibrin represents, for the normal tissue, simply so much foreign material from which it must free itself by digestion; as long as the autolysis of this foreign mass proceeds slowly, higher and toxic split products will be absorbed as such; digestion proceeds slowly, because the leukocytes are still living, and therefore not "shedding" their ferment as they should, and because of the great increase in the antiferment of the serum and tissue fluids which takes place early in the infection. According to the hypothesis presented, if the antiferment titer is now lowered and at the same time sufficient protease and peptidase are liberated, we might expect a temporary increase in the degree of intoxication (because of the rapid absorption of toxic split products) followed by a detoxication when autolysis is actively initiated. A therapeutic ideal might therefore be sought in just such an alteration of the ferment-antiferment balance.

Let us assume, on the other hand, that we are dealing with a quiescent tubercle with just sufficient encapsulation by scar tissue to prevent any excretion of toxic material from the focus. If, for any reason, the serum alteration above mentioned should occur in such a patient, we might expect a considerable degree of intoxication due to the digestion of the protective connective tissue and of the central necrotic mass, together with the liberation of accumulated toxic material preformed in the necrotic focus. Theoretically, it might seem warranted to endeavor to increase the antiferment in this condition in order to check protease activity and protect the tubercle from digestion. In a subsequent article this reaction and its relation to our present empirical therapy will be discussed in detail. It will be evident from the two examples outlined that fluctuations in the digestive balance of the tissues and serum may effect certain pathologic processes in a most fundamental way.

When considering the factors in the balance, it is apparent that we are compelled to consider the antiferment, or antitrypsin, as it is commonly designated, as an integral part of the mechanism under consideration. Here we enter the field of lipoid bodies. The antiferment is not an antibody in the immunologic sense, although it was early so

considered; it consists of the highly dispersed unsaturated lipoids of the serum and lymph and its titer varies, therefore, with at least three conditions: (*a*) the amount of lipoids present; (*b*) the dispersion, and (*c*) the chemical structure; that is, the degree of unsaturation; all conditions that are subject to considerable variation and any one of which may account for wide fluctuations in the titer commonly observed. Thus, lessening the dispersion by acidifying, by salting and by heating to a sufficient degree, inactivates the antiferment; physical adsorption by certain chemically inert adsorbing surfaces lowers the titer; solution of the lipoids in chloroform and ether removes the antiferment from the serum. The most comparable substances, in their antitryptic property, which we have available, are the soaps of the unsaturated fatty acids. There is considerable ground for the belief that the antiferment lipoids are in more or less intimate physical combination with the serum albumin with which fraction they are thrown down on the usual methods of separation of the serum proteins.

It is known that the antiferment is greatly augmented during certain diseases, notably in the acute infections, in pregnancy, in carcinoma and cachectic states in general; following anaphylactic and other protein shock, and in certain pathologic processes in the central nervous system of a degenerative character; in other words, it forms part of a rather general "reaction" phenomenon. This seems purposeful, in that an increase in the antiferment power would tend to counteract the heightened destruction of the proteins of the body commonly observed in toxic conditions. The antiferment of the lymph stream is appreciably increased after feeding, although the increase in the blood stream is only moderate in amount; in starvation, on the other hand, the antiferment shows a progressive decrease.

We deal, then, with the probability that the antiferment may be augmented by selective diet, by shock therapy (including vaccines), and possibly by the intravenous injection of the proper lipoids. Another factor enters, however, into the regulatory mechanism, namely, the fact that the amount of lipoids in the serum is related to the lipolytic activity developed therein. That is, when the lipolytic activity is low, as for instance, in pregnancy, in carcinoma, in the acute infections and in advancing tuberculosis, an accumulation of lipoids will take place in the serum and, as a corollary, the antiferment titer will increase. Conversely, a strengthening of the lipolytic activity will metabolize the serum lipoids more rapidly and in this way decrease the antiferment titer. It is apparent, therefore, that the regulation of the antiferment titer is dependent on several factors, some of which may be amenable to artificial and therapeutic control.

Empirically, we have probably been doing precisely this in our use of iodin and the iodids. These are used therapeutically in a great

number of disease conditions, but chiefly, and with universal acceptance, to hasten the resolution of necrotic tissues, such as the gummas of late syphilis. It has been demonstrated experimentally that the iodids will increase the rate of autolysis to a considerable degree. Inasmuch as the effect is not found to be directly on the ferment, we must seek to find some other explanation. In this connection it was noticed in vitro experiments that the iodids lessened the antiferment titer of the serum, and later experiments carried out in clinical cases revealed that a lowering of the antiferment titer took place progressively under iodid therapy. We have then, it seems, one of the means of influencing the ferment-antiferment balance in common use.

The direct intravenous injection of ferments has not yet been used with success, because of the toxicity of the perparations employed. Hiss and Zinsser, in their interesting work commenced a number of years ago, employed leukocytic extract subcutaneously with encouraging results, although the possibility is not excluded, as Zinsser and Tsen point out in a recent article, that the results achieved are due to a general shock reaction rather than to the absorption of ferments. The direct increase of ferments is at least one method of approach worthy of further investigation.

If protein splitting with its resulting formation of toxic split products is at the basis of many of the intoxications with which we have commonly to deal in acute and chronic conditions, then the detoxication by means of ereptases and similar ferments should be of considerable importance. From experimental observations it seems probable, at any rate, that by means of alterations in the ferment-antiferment balance we may be able to attack certain therapeutic problems from this relatively simple point of view.

THE RELATION OF PELLAGRA TO LOCATION OF DOMICILE IN INMAN MILLS, INMAN, S. C.*

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INTRODUCTION

In the immediately preceding paper[1] of this series, the section of this report dealing with geographical distribution of pellagra was begun by a detailed study of the relation of pellagra to domicile in Spartan Mills. That community was regarded as a fairly typical cotton mill village, but nevertheless it presented certain individual peculiarities. It was situated within the limits of a fairly large city. It was one of the oldest mills in the county. It possessed an organized social service for education of the people and a good hospital for the care of the employees. Very marked general sanitary improvements were made during 1913 and 1914, during the progress of our study there. The early history of pellagra in the village was obscure and the records of the population previous to the fall of 1913 were incomplete. Inman Mill Village may be contrasted with Spartan Mills in respect to these features. This mill village is located about twelve miles from Spartanburg City, near a small country station. It is one of the newer mills of the county, having been constructed in 1902. There was no provision for social service. The general sanitary arrangements of the community have remained much the same since the erection of the mill. The available records in regard to population within the mill village are exceptionally complete, in part, because a

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* From the Robert M. Thompson Pellagra Commission of the New York Post-Graduate Medical School and Hospital.

* This is the eleventh paper in the series now appearing in THE ARCHIVES, constituting the third report of the Robert M. Thompson Pellagra Commission. This paper has been written since Dr. Garrison and Dr. Siler were recalled to active service in the Medical Corps, U. S. Navy, and the Medical Corps, U. S. Army, respectively. They are, therefore, not responsible for the compilation of the data, nor for the deductions drawn from them.

1. The Relation of Pellagra to Location of Domicile in Spartan Mills, S. C., and the Adjacent District, THE ARCHIVES INT. MED., 1917, **20**, 198.

permanent record of the tenants in the various houses has been kept in the office of the mill company, and, in part, because a house-to-house census of this village was made by us in 1912, a year earlier than in Spartan Mills. Because of these general differences from Spartan Mills, it seems important to present the detailed data in regard to the domiciliary relationship of pellagra in Inman Mill Village.

GENERAL DESCRIPTION OF THE VILLAGE

The community of Inman Mills[2] is situated in Campo Bello and Beech Springs Townships of Spartanburg County, about half a mile from Inman Station on the Asheville-Columbia division of the Southern Railroad and about twelve miles from Spartanburg City. There is a

Fig. 1.—General view of Inman Mill Village looking southeast. The house in the middle foreground of the picture is 2 C Street.

small country village surrounding the railroad station, which provides a commercial and shipping center for the surrounding farming district. The mill village is a separate community and is surrounded by farms.

Previous to 1902 the site of the present mill was farm land. The mill was erected in 1902 and put into operation in September of that year. The motive power is steam and the manufactured products are the heavier grades of cotton cloth.

At the time when the mill was first opened in September, 1902, most of the houses situated on A, B, C, D and the north side of E

2. We are indebted to Mr. James A. Chapman, President of Inman Mills, for important information used in this section.

Fig. 2.—A typical house at Inman Mills. This is a front view of 17 D Street.

Fig. 3.—The two types of wells supplying water for domestic purposes at Inman Mills.

Streets were built and ready for occupancy. Three dwellings for negroes were also erected across the railroad track. In the following years houses were added on C, D and E Streets; in 1907, F Street was opened with 23 new houses and in 1913, G Street was opened with 10 houses on the north side, bringing the total number of dwellings to 120 in 1914. The mill houses are all of frame construction, built without cellars, most of them containing four or six rooms and arranged to accomodate two families. Besides the mill houses and the mill, the

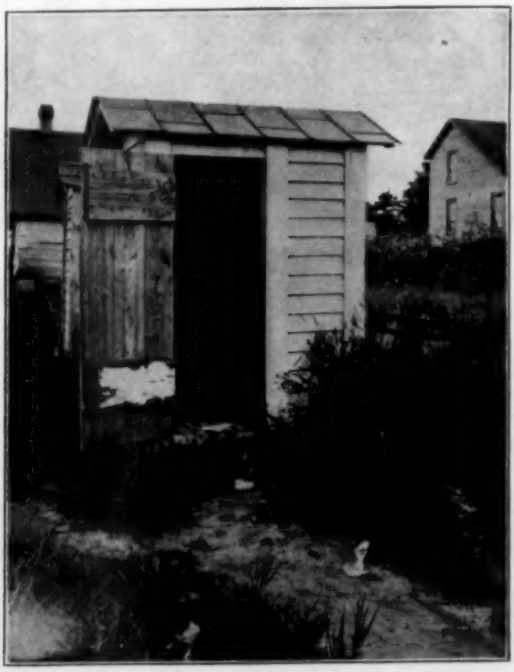

Fig. 4.—Front view of a typical outhouse at Inman Mills. The type of garbage receptacle is also shown.

village contains a chapel situated on A Street, a store, a ten-room boarding house, designated as a hotel, and the superintendent's house on B Street.

Water for technical use and for fire protection is stored in a standpipe at the upper (east) end of C Street (See map, Fig. 5). The water for domestic use is obtained from wells, part of them driven wells with pumps and part of them open wells with chain and bucket.

The location of these wells is indicated on the map. The method of disposal of human excreta is by means of open surface privies, provided, in part, with metal pails. Ultimate disposal is by scavenger service. The location of the privies is indicated in Figure 1 and also on the map (Fig. 5).

A general view of the village is shown in Figure 1. A typical house is shown in Figure 2. Figures 3 and 4 show the types of wells and the type of privy, respectively.

Insects.—The house fly (*Musca domestica*) is very abundant during the warmer season. The stable fly (*Stomoxys calcitrans*) is present in considerable numbers. During 1912, 1913 and 1914 the cows were kept in a pasture separate from the dwelling houses, but nevertheless the stable flies were usually present about the houses and often constituted a pest to persons on the porches. The bedbug (*Cimex lectularius*) is present in practically every house, and construction of the houses makes its eradication very difficult. The head louse (*Pediculus capitis*) is common on the children. Practically every child had been infested with this parasite at some time. Especially the children in school and those at work in the spinning room of the mill are commonly infested. The body louse (*Pediculus vestimenti*) has not been observed and the people appear not to be acquainted with it. The sand fly (*Simulium*) has not been observed in this village, although there are potential breeding places in the vicinity.

Population.—At Inman Mills the population was drawn chiefly from the neighboring mill villages and from the outlying farms. The inhabitants were of the usual mill type found in these villages. A noticeable feature of these people was their migratory tendency. Because of inefficiency, through ignorance or general inferiority, they easily became discontented and roamed from mill to mill, staying at a town only a few months, or even weeks. A large proportion of the residents at Inman in each year consisted of these transients. Moreover, of the more permanent residents of the village many moved about from house to house within the town. It was, therefore, not surprising to find that a single house list often contained the record of as many as five or six families during one year. In fact, of the 118 families canvassed in 1912, the first year of our census, only 26 still occupied the same house in October, 1914.

The tendency to change residence was observed in pellagrous as well as in nonpellagrous households. Of the twenty-four pellagrins incident at Inman in 1912 and 1913, only nine remained continuously in the same house from onset to the end of our survey. This migratory

tendency of the population, as a whole, will explain in great part the comparatively large size of the second zone in each year.

In Table 1 the total white population, as recorded in our three house-to-house canvasses, is shown distributed according to sex and age in each year, 1912 to 1914, inclusive. It may be noted that the yearly totals in Table 1 represent only those persons actually present in the village during the respective census. These population totals do

TABLE 1.—Distribution of the White Population of Inman Mills, According to Sex and Age, in Each Year

Age	1912			1913			1914		
	Female	Male	Total	Female	Male	Total	Female	Male	Total
0- 4	44	55	99	54	77	131	57	65	122
5- 9	45	39	84	44	54	98	49	57	106
10-14	30	23	53	35	23	58	42	33	75
15-19	27	31	58	45	34	79	46	29	75
20-24	22	16	38	47	43	90	35	29	64
25-29	16	12	28	25	23	48	29	14	43
30-34	12	25	37	24	33	57	19	31	50
35-39	12	7	19	14	18	32	24	23	47
40-44	4	4	8	10	13	23	10	14	24
45-49	5	4	9	7	5	12	6	11	17
50-54	2	2	4	4	7	11	7	5	12
55-59	6	1	7	7	2	9	6	5	11
60-64	3	3	6	5	6	11	4	7	11
65-69	0	1	1	3	2	5	4	0	4
70-74	1	0	1	1	1	2	0	1	1
75-79	0	0	0	0	0	0	0	0	0
Over 80	0	0	0	0	0	0	0	0	0
Age unknown	81	93	180*	5	12	17	2	2	4
Total	310	316	632*	320	353	673	340	326	666

* Including six individuals whose age and sex were not ascertained.

not correspond, therefore, to those shown in Tables 12, 13 and 14 (summarized in Table 11), which include the entire number of individuals recorded in the mill house lists during the respective year. The average size of families among these mill workers was five persons.

The colored population in this town was very small, as shown in Table 2. With few exceptions, negroes were not employed as house servants in this village, although some of the colored women did cook-

ing and laundry work for the residents. The adult negro males were laborers or engaged in heavy work about the mill.

Industrial and Economic Conditions.—The wages paid at this mill have been somewhat lower than at Spartan Mills. In July, 1914, the mill employed 183 men over 16 years of age, fifty-three boys under 16 years, seventy-seven women over 16 years of age and twenty-eight girls under 16 years. The average daily wage in this month was $1.15

TABLE 2.—DISTRIBUTION OF THE NEGRO POPULATION OF INMAN MILLS, ACCORDING TO SEX AND AGE, IN 1913 AND 1914

Age	1913			1914		
	Female	Male	Total	Female	Male	Total
0- 4	0	1	1	2	0	2
5- 9	0	1	1	2	1	3
10-14	3	0	3	3	1	4
15-19	0	4	4	1	4	5
20-24	0	0	0	1	0	1
25-29	0	0	0	2	0	2
30-34	0	0	0	1	0	1
35-39	1	1	2	0	0	0
40-44	1	0	1	1	1	2
45-49	0	0	0	1	0	1
50-54	0	1	1	0	2	2
55-59	0	0	0	0	0	0
60-64	0	0	0	0	0	0
65-69	0	0	0	1	0	1
70-74	0	0	0	0	0	0
75-79	0	0	0	0	0	0
Over 80	0	0	0	0	0	0
Age unknown	0	0	0	0	0	0
Total	5	8	13	15	9	24

for the men, 58 cents for the boys, 87 cents for the women and 63 cents for the girls. The relation between the mill company and its employees is closer here than at Spartan Mills, because the mill and its village form a definite unit rather isolated from other communities. A large share of the supplies for the people are handled by the company store because it is the only one close at hand.

General Dietary.—The dietary was investigated by personal interview at the home of every family in 1912 and 1913, and dietary

changes were inquired into in 1914. In general, it may be said that the diet differs from that of the people in Spartan Mills by approaching the diet of the rural population. Much less fresh meat was eaten at Inman Mills during the years of our inquiry. On the other hand, more than half the families kept a cow and chickens and the use of milk and eggs was much greater here. Practically every family had a large garden, the allowance of ground space being more ample than at Spartan Mills. Compound lard, containing cottonseed oil, was used

TABLE 3.—Distribution of the White Mill Operatives Residing in Inman Mills, According to Sex and Age, in 1913 and 1914

Age	1913			1914		
	Female	Male	Total	Female	Male	Total
Under 12	1	1	2	1	0	1
12-14	17	10	27	12	17	29
15-19	32	39	71	37	24	61
20-24	21	46	67	21	27	48
25-29	5	21	26	9	11	20
30-34	8	31	39	5	29	34
35-39	1	21	22	4	23	27
40-44	0	8	8	1	13	14
45-49	0	3	3	0	7	7
50-54	1	5	6	0	1	1
55-59	0	0	0	0	4	4
60-64	0	3	3	0	3	3
65-69		3	3		0	0
70-74	0	1	1	0	1	1
75-79	0	0	0	0	0	0
Over 80	0	0	0	0	0	0
Age unknown	5	4	9	1	4	5
Total	91	196	287	91	164	255

by every family in Inman Mills in 1913. In other respects the dietary was not different from that of the population at Spartan Mills. The frequency of use of certain articles of diet in this village has been discussed in detail in our Second Progress Report, where Inman Mills was designated as Mill Village 1.

Prevailing Diseases.—The acute infections of childhood prevailed in epidemic form every few years. Diarrhea and dysentery were prevalent throughout the warm season, among both children and

adults. Local epidemics of typhoid fever were frequent, usually attacking several families in neighboring houses, while the rest of the village escaped. Pulmonary tuberculosis and hookworm disease were not observed. Indigenous malaria did not occur.

HISTORY OF PELLAGRA AT INMAN MILLS IN THE YEARS PREVIOUS TO 1912

The first known case of pellagra at Inman Mills was Pellagrin 37, a woman aged 32 years, who developed an initial erythema at 3 E Street in 1908. The exact time of onset in this case is not quite certain, for although the patient says that her erythema appeared while living in this house in the fall of 1908, the mill records show that the family resided at 3 E Street only until Aug. 31, 1908. It is, therefore, most probable that Pellagrin 37 actually developed the disease sometime earlier in the summer of that year. The only recorded symptom in this first attack was the characteristic erythema, which appeared on the hands "after washing with Gold Dust," and did not subside until well into the winter. Pellagrin 37 had lived at Inman Mills since 1903 and in this particular house since Feb. 13, 1907, although her husband told us that prior to onset of pellagra, she had made frequent long visits at her mother's house in another mill village conspicuous for its many cases of pellagra. On Aug. 31, 1908, Pellagrin 37 moved to 13 E Street, where she resided until Nov. 15, 1908, when she removed to 24 F Street. She is indicated on the map (Fig. 5) at 3 E Street, the house of origin, by a solid circle and at the two subsequent residences by hollow circles. There were no other known cases of pellagra at Inman in 1908.

In 1909 Pellagrin 37 suffered a recurrence in the spring, while living at 5 D Street, where she had moved on Jan. 16, 1909. She went to the State Hospital for the Insane at Columbia, July 15, 1909, and except for brief visits at home, she remained there until April, 1911. Her residence at 5 D Street has been indicated by a hollow circle on the map (Fig. 5), and her residence at 24 F Street, although of only fifteen days' duration in 1909, has been designated likewise. A second case of pellagra appeared in this village during this year. At 1 C Street Pellagrin 318, a man aged 52 years, developed his initial erythema in July, 1909. He was a millworker who had lived in Inman Mills since 1904 and in the house at 1 C Street for more than two years. Early in the spring, 1909, he began to be troubled with diarrhea, which was later followed by erythema of the hands, with several repetitions of redness and peeling, accompanied by a persistent sore mouth. He was taken to Columbia for treatment, remaining there until January, 1910. On the map (Fig. 5), Pellagrin 318 has been indicated by

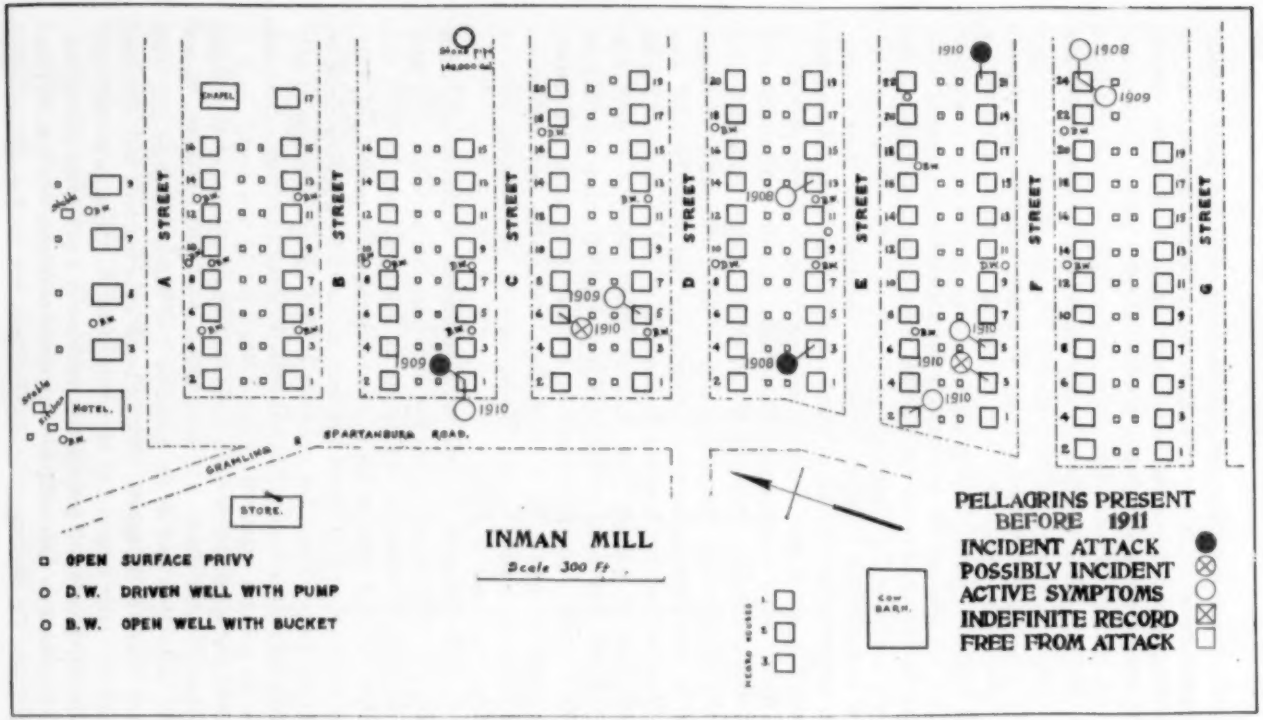

Fig. 5.—Map of Inman Mills showing the location of houses, wells and privies. Pellagrins present previous to 1911 are indicated on this map in red. The year of residence is also indicated.

a solid circle at the house of origin, 1 C Street. These two cases, Pellagrins 37 and 318, are the only pellagrins definitely known to have resided at Inman Mills in 1909.[3]

In 1910 Pellagrin 318 died of pellagra at his home at 1 C Street, shortly after his return from the hospital at Columbia. Pellagrin 37, who had been at the Columbia State Hospital since the previous summer, suffered a recurrence in the spring, 1910. She returned to her family, who were living at 5 F Street, in the latter part of April, but within a week's time was obliged to go back to Columbia. In July, 1910, she returned to Inman Mills and stayed at 5 F Street with her family until Oct. 15, 1910, when they all moved to 2 E Street. Again in December, 1910, Pellagrin 37 went to Columbia for treatment, remaining there until April, 1911. Pellagrins 318 and 37 have been designated at their respective residences in 1910 by hollow circles on the map (Fig. 5). There was one case of pellagra apparently incident at Inman Mills in 1910, namely, Pellagrin 366, a woman aged 24, who developed an initial erythema at 21 F Street. She had lived in this house since Feb. 1, 1910, coming here from another mill village in which pellagra was very prevalent. Details in regard to this first attack are lacking, but it is possible that the origin of this case was outside of Inman Mills. Pellagrin 366 has been designated, however, by a solid circle at 21 F Street, the apparent house of origin. Another patient who may possibly have contracted pellagra at Inman Mills in 1910 was Pellagrin 883, a woman aged 31 years, who developed her initial erythema in April, 1911. She lived at 6 C Street from March 1, 1910, until Jan. 5, 1911. From this house, which may be the house of origin, she went to live on a farm outside of Inman Mills and her initial attack occurred at this latter residence. She has been indicated at 6 C Street by a circle containing a cross. At 3 F Street Pellagrin 198, a man aged 40 years, resided from June 4, 1910, to Nov. 30, 1910, in next-door relationship to Pellagrin 37, who lived at 5 F Street and later at 2 E Street. From Inman Pellagrin 198 moved to 397 Arch Street, Spartan Mills, where he remained until January, 1911. In January, 1911, he moved to 343 College Street in the same village. His initial erythema appeared during a short stay at Liberty Mill in March,

3. At 10 D Street Pellagrin 333, an elderly woman, lived with her daughter during the fall and winter, 1909 and 1910. From March 16, 1910, to May 15, 1911, the family lived at 3 D Street. Late in the winter, 1911, they moved to 12 C Street and remained there until Jan. 12, 1912, when the mother left Inman Mills and went to live with one of her sons, at whose house she died of pellagra, June 15, 1912. According to her daughter's statement, Pellagrin 333 had suffered from the disease since 1908 and it is probable that she was an old case. Our information, however, seems too meager to permit of a diagnosis earlier than 1912, in which year she is known to have died of pellagra, and she has, therefore, not been included as a pellagrin at Inman Mills.

1911, within four months of the termination of his exposure at Inman Mills. He has been considered possibly incident at each of the three residences cited above, but in all probability the actual house of origin was 3 F Street, where he has been indicated by a circle containing a cross. There were no other definite cases of pellagra known to be at Inman in 1910.[4]

In 1911 several pellagrins who had contracted the disease elsewhere moved to Inman Mills. Pellagrin 514, who had had her initial attack in that summer, came to live at 1 A Street, Dec. 10, 1911. At 9 F Street Pellagrins 91 and 93, both of whom had shown active symptoms earlier in the year, resided from Nov. 22, 1911, to the end of that year. Pellagrin 163 lived at 13 F Street from Sept. 21, 1911, until the following spring. She had a recurrence in 1911 and again in 1912. Pellagrin 726, incident earlier in the summer at Spartan Mills, lived at 18 F Street from June 29, 1911, until Sept. 30, 1911. Pellagrin 145, who had her initial attack in 1904 and had suffered recurrences each spring thereafter, moved to 17 D Street Dec. 4, 1911. Pellagrin 328, who had developed some premonitory symptoms of pellagra at Spartan Mills, came to 9 E Street Nov. 16, 1911, and suffered her initial erythema here early in 1912. These seven cases have been indicated at their respective residences by hollow circles on the map (Fig. 6). In addition to these moved-in cases there were two old resident pellagrins at Inman Mills in 1911, namely, Pellagrin 37, who returned from Columbia in April, 1911, to her home at 2 E Street, and Pellagrin 366, who lived at 21 F Street until Aug. 31, 1911, and subsequently at 22 F Street until the middle of November, 1911, when she moved from the village. Both of these patients suffered recurrences in 1911 and have been indicated at their respective residences by hollow circles on the map (Fig. 6).

There were four pellagrins incident at Inman Mills in 1911. Pellagrin 319, aged 32 years, was the daughter of Pellagrin 318, who had died at 1 C Street in January, 1910. During the year following her father's death, Pellagrin 319 had not been strong, but she had not shown any definite pellagrous erythema until the spring of 1911. She died at her home at 1 C Street Aug. 13, 1911. A second case incident at this mill was Pellagrin 160, a girl 17 years old, who showed an initial erythema in June, 1911, at 16 C Street, where she had lived since Oct. 1, 1910. The third case was Pellagrin 592, a woman aged 19 years,

4. Pellagrin 329, mother of Pellagrins 198, 326 and 328, frequently visited a son at Inman Mills during his residence at 10 F Street from May, 1910, to February, 1911. It is possible that she was a pellagrin at this time, although, for lack of definite information, she has been classed as incident later in 1911 at Spartan Mills. She is known to have had a definite attack of pellagra which ended fatally in October, 1911.

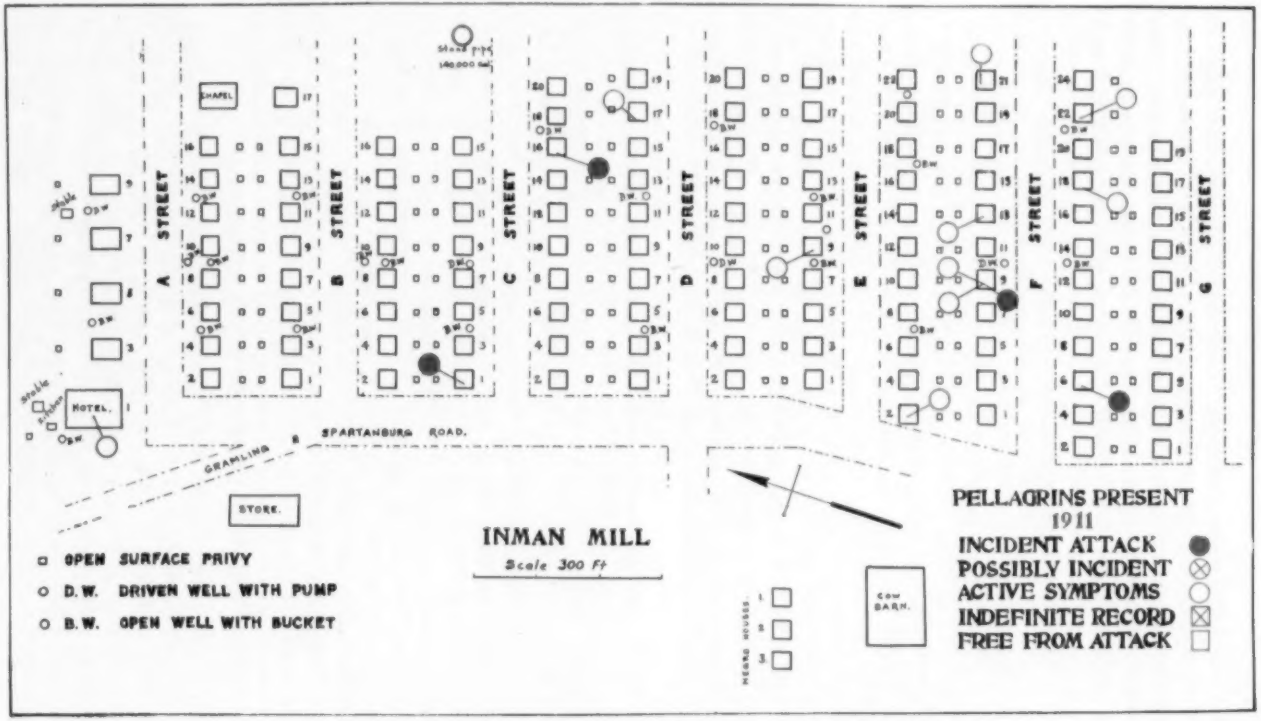

Fig. 6.—Map of Inman Mills, showing pellagrins present in 1911.

who developed initial symptoms of the disease in June, 1911, at 9 F Street, where she had been living since Jan. 18, 1911. Previous to this residence she had lived in a town where pellagra was prevalent. She moved away from Inman Mills Aug. 31, 1911, but returned in 1913. A fourth case, probably incident in this year, was Pellagrin 316, a man

TABLE 4.—Pellagrins Residing in Inman Mills in Each Year From 1908 to 1911, Inclusive

Pellagrins	1908	1909	1910	1911	Sum
Definitely incident	1	1	1	4	7
Possibly incident	0	0	2	0	2
Recurrent	0	1	2	8	11
Without symptoms	0	0	0	0	0
With indefinite record	0	0	0	0	0
Total	1	2	5	12*	20

* Pellagrin 328 has not been included in this table. She appears to have contracted pellagra at Spartan Mills in 1911, and she moved to Inman Mills in November, 1911, where her initial erythema appeared early in 1912

TABLE 5.—Pellagrins Incident in Inman Mills in Each Year From 1908 to 1911, Inclusive

House	Residence Period	Onset	Pellagrin	Sex	Age
3E	Feb. 13, 1907 – Aug. 31, 1908	Summer, 1908	37	F	32
1C	Jan. 26, 1907 – Jan., 1910	July, 1909	318	M	52
6C	Mar. 1, 1910 – Jan. 5, 1911	April, 1911	883*	F	31
3F	June 4, – Nov. 30, 1910	March, 1911	198*	M	41
21F	Feb. 1, 1910 – Aug. 31, 1911	1910	366	F	24
1C	Jan. 26, 1907 – Aug. 13, 1911	Spring, 1911	319	F	32
16C	Oct. 1, 1910 – Mar. 31, 1912	June, 1911	160	F	17
6F	Feb. 16, 1910 – Aug., 1911	1911	316	M	65
9F	Jan. 18, 1911 – Aug. 31, 1911	June, 1911	592	F	19

* Origin probably here; first erythema appeared after moving away.

aged 65 years, who had lived at 6 F Street since Feb. 16, 1910. He died of pellagra in August, 1911. It is possible that he had the disease in 1910, but he has been classed in 1911 for lack of more definite history. These four incident cases have been indicated at their respective residences by solid circles on the map for 1911 (Fig. 6).

Table 4 presents a summary of the pellagrins definitely known to have resided at Inman Mills in the years preceding 1912. The data

for these earlier years are incomplete, as our field work at this mill did not commence until 1912. The pellagrins whose incidence may be traced with some degree of certainty to residence in this mill village are summarized by apparent house of origin in Table 5 for all years to 1911, inclusive. No attempt has been made to correlate incidence of pellagra with location of domicile in these earlier years, although when antecedent pellagra has existed in the immediate vicinity, it has been noted so far as the records permit.

THE DOMICILIARY RELATIONSHIP OF PELLAGRA IN 1912

Our field work at Inman Mills began in July, 1912, and this particular community was more intensively studied than any other in that year. The first house-to-house canvass and census of the population was made at Inman Mills in 1912, an intensive method of study which was first applied to other communities in 1913. The data for the year 1912 are, therefore, more accurate and more complete here than for other villages, but, of course, considerably less complete even for Inman Mills than for the year 1913, because the work began rather late in the pellagra season of 1912 without any previous study of this population.

The data for the year 1912 are presented in detail in Table 12. Each house has been set down in turn and its occupants have been assigned to Zone 1, Zone 2 or Zone 3, in accordance with the rules adopted for the domicile study. The zone relationship has been determined entirely by the relation of domicile to an active case of pellagra: that is, to a pellagrin who manifested activity of the disease in the respective year or in the immediately preceding year. Pellagrins who had been free from attack of the disease for two years were excluded from consideration as centers for this zone study. Those nonpellagrous persons who resided in the same house with an active pellagrin for a period of at least two weeks in 1912 were assigned to Zone 1 in this year. If any one of these persons developed an attack of the disease later than two weeks after the beginning of domiciliary exposure and within a reasonable period after the termination of such exposure, the incidence of the disease was credited to Zone 1. This reasonable period has been arbitrarily limited to three months during the warmer season, from April 1 to October 1, and to six months, when all or part of the period fell in the colder season, from October 1 to April 1. Those nonpellagrous persons who resided in a house next door to an active pellagrin for a period of at least two weeks were assigned to Zone 2, unless, because of preceding and subsequent residence in Zone 1 within the reasonable incubation period, they were still considered as subjects of that zone. Any cases developing among these persons later than two weeks after the beginning of the exposure and within a reasonable

period after its determination have been credited to Zone 2. Those nonpellagrous persons who resided in this community in a house farther away than next door from an active pellagrin, have been assigned to Zone 3, unless, because of definitely known preceding and subsequent residence in Zone 1 or Zone 2 within the reasonable incubation period, they were still considered as subjects of either of these zones. Any cases of pellagra developing among these persons have been assigned to Zone 3. This plan is the same as that followed in the domiciliary study of Spartan Mills,[1] presented in the immediately preceding paper of this series, where fuller discussion of this plan may be found. It will be noted that pellagrins for whom the records are incomplete would tend to fall into Zone 3, because cases without known domiciliary association have been placed here.

During 1912 there were ten pellagrins residing at Inman Mills who had suffered from the disease in a previous year or who were incident elsewhere. Eight of these were living at Inman Mills early in the year and the two others moved in after the pellagra season. These cases are indicated by hollow circles on the map for 1912, Figure 7. One of them, Pellagrin 328, came to 9 E Street from Spartan Mills Nov. 16, 1911. At the previous residence she had nursed her mother, Pellagrin 329, until her death from pellagra in October, 1911. The daughter suffered from sore mouth and diarrhea at Spartan Mills, but the diagnosis of pellagra was not considered to be definite until early in the spring of 1912, when she developed an erythema on the backs of her hands while residing at 9 E Street, Inman Mills. It is possible, however, that she did have an erythema at Spartan Mills in 1911. The interval between the termination of the first-zone exposure at Spartan Mills and the appearance of the erythema at Inman Mills was less than six months in any case, and she has, therefore, been considered incident at the earlier residence and has been designated as a pellagrin moving into Inman Mills with the disease. She moved from 9 E Street to 12 D Street April 30, 1912, and is designated by a hollow circle at both these houses. Pellagrin 636 came to 24 F Street Oct. 24, 1912, having suffered a recurrent attack of pellagra earlier in the year at a farm in another part of the county. Seven of the other pellagrins suffered recurrences of pellagra at Inman Mills in 1912. Some of them moved during the year, so as to appear at more than one place on the map. Pellagrin 160 moved from 16 C Street to 3 C Street. Pellagrin 163 is shown at 13 F Street and again at 5 B Street, where she visited. Pellagrin 883, who had her first erythema in 1911, remained free from symptoms of pellagra during 1912 and is indicated by a hollow square at 7 F Street. Three pellagrins incident at Inman Mills in 1912 subsequently moved into other houses and are there designated by hollow

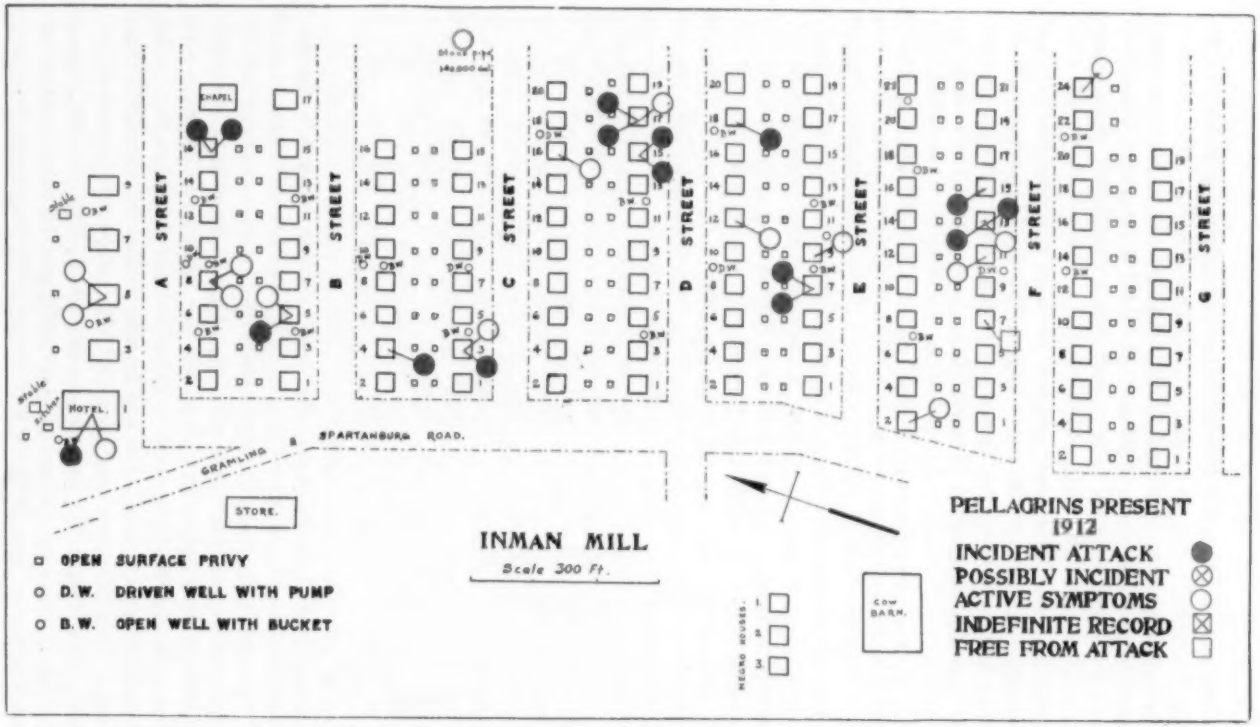

Fig. 7.—Map of Inman Mills showing pellagrins present in 1912. Note the foci of the disease at 3 C, 17 D, 9 E and 13 F Streets.

circles, namely, Pellagrins 150 and 315 at 5 A Street and Pellagrin 280 at 11 F Street.

According to the detailed data of Table 12, there were sixteen pellagrins incident at Inman Mills in 1912. Brief data in regard to these cases are summarized in Table 6, and they are indicated on the map for 1912, Figure 7, by solid red circles.

Six of these have been assigned to Zone 1. Pellagrin 113, an unmarried woman aged 20 years, came to the boarding-house at 1 A Street April 10, 1912. She had been at Inman Mills for eight months and had been living at 15 D Street previous to April 10, next door to

TABLE 6.—PELLAGRINS INCIDENT AT DEFINITE HOUSES AT INMAN MILLS IN 1912

House	Residence in House	Zone	Residence in Zone	Onset Date	Pellagrin	Sex	Age
1A	Apr. 10, 1912 - Aug., 1912.....	1	Apr. 10, 1912 - June 25, 1912	July 14, 1912	113	F	20
16A	Since Nov. 1, 1906.....	3	1907 - June, 1912.....	June, 1912	182	M	47
16A	Since Nov. 1, 1906.....	3	1907 - June, 1912.....	June, 1912	157	M	6
4B	Since Mar. 10, 1910.....	2	Apr. 1, 1912 - June, 1912.....	June, 1912	164	F	30
5B	Since Apr. 24, 1911.....	2	Jan. 1, 1912 - July 1, 1912...	July 1, 1912	114	F	18
8C	Since Apr. 1, 1912.....	1	Since June, 1911.....	June, 1912	161	F	56
15D	Since Jan. 1, 1911.....	2	June, 1911 - July 15, 1912....	July 15, 1912	148	M	6
15D	Since Jan. 1, 1911.....	2	June, 1911 - July 15, 1912....	July 15, 1912	149	M	4
17D	Since Dec. 4, 1911.....	1	Since spring, 1904.....	Aug. 1, 1912	146	M	6
17D	Since Dec. 4, 1911.....	1	Since spring, 1904.....	Aug. 1, 1912	147	M	3
18D	May 14, 1912 - June 13, 1912....	2	July 1, 1911 - June 13, 1912..	July, 1912	280	F	19
7E	Since Nov. 23, 1911.....	1	Since Apr., 1912.....	June, 1912	158	F	7
7E	Since Nov. 23, 1911.....	2	Spring, 1912 - Apr., 1912....	Apr., 1912	154	F	5
12F	Sept., 1911 - Mar. 18, 1912.....	1	June, 1909 - Mar. 18, 1912....	Summer, 1912	884	F	20
12F	June 18, 1912 - Aug. 20, 1912....	2	July, 1912 - Aug. 20, 1912....	Aug. 21, 1912	315	F	20
15F	Mar. 13, 1912 - July 18, 1912....	3	Mar. 18, 1912 - Aug. 1, 1912..	Aug. 1, 1912	150	F	16

a pellagrin at 17 D Street and one at 16 C Street. At 1 A Street she was in the same house with Pellagrin 514, who suffered her first attack in 1911 and a recurrent attack in May, 1912, shortly after the arrival of this young woman. Pellagrin 514, who was the woman in charge of the boarding-house, left June 25, 1912. Pellagrin 113 had a sore mouth during the latter part of June and she developed her initial erythema July 14, 1912. She was brought to the Post-Graduate Hospital in New York for treatment and has remained free from recurrence since 1912. The second case in Zone 1, Pellagrin 161, was a woman 56 years old, whose daughter, Pellagrin 160, had suffered an initial attack in June, 1911, at 16 C Street. The family lived at 16 C

Street until April, 1912, and then moved to 3 C Street. The daughter, Pellagrin 160, suffered a recurrent attack in June, 1912, and the mother, Pellagrin 161, had her initial attack in the same month. The third and fourth cases in Zone 1, Pellagrins 146 and 147, were brothers, aged 6 years and 3 years, respectively. They had lived at 17 D Street since Dec. 4, 1911. Their mother, Pellagrin 145, had her initial attack in 1904 and had suffered recurrences every year since. Both children developed pellagra about Aug. 1, 1912. The older boy had the erythema on his hands and feet, while the younger, Pellagrin 147, showed the erythema only on the feet. In 1913 these children remained free from manifestations of pellagra, but in 1914 they both had mild recurrences of the disease. The fifth case in Zone 1 was Pellagrin 153, a girl 7 years old, living at 7 E Street. Her sister, Pellagrin 154, suffered her initial attack of pellagra about April 1, 1912, and this little girl, Pellagrin 153, developed the disease in June, 1912, more than two months later, while living in the same house. The sixth case in Zone 1, Pellagrin 884, a woman aged 20 years, lived with her mother, Pellagrin 163, at 13 F Street from Sept. 21, 1911, to March 18, 1912. She then went to a farm a few miles away, where she developed her initial erythema in the summer. The exact date of the appearance of the erythema was not ascertained, and there is no record of possible association with pellagrins at the new residence at the farm. The case has, therefore, been designated as incident in Zone 1 at 13 F Street.

The total number of exposed persons in Zone 1 in 1912, according to Table 12, was 129. The appearance of six new cases of pellagra in this zone indicates, therefore, an incidence rate of 4.65 per cent.

Seven of the incident pellagrins in Table 6 have been assigned to Zone 2. Pellagrin 164, a woman 30 years old, suffered her initial attack at 4 B Street in June, 1912. She had resided in this house since March 10, 1910. In 1911 her house was in next-door relationship to Pellagrin 319 at 1 C Street, who had an initial attack early in 1911, ending in death in August, 1911. Again, after April, 1912, her house came into the second zone, because Pellagrin 160 moved to 3 C Street in that month. About two months later, Pellagrin 164 suffered her initial attack in the house at 4 B Street, directly behind 3 C Street and adjacent to it. The second case in Zone 2, Pellagrin 114, a girl 18 years old, had lived at 5 B Street with her parents since April, 1911. From Jan. 1, 1912, until March 27, 1912, her home was in next-door relationship to Pellagrins 91 and 93, who lived at 8 A Street during that time. Her residence came again into the second zone in June, 1912, when Pellagrin 164 developed her initial erythema at 4 B Street. Pellagrin 114 had her initial erythema July 1, 1912, and has been designated as incident in the second zone in relation to Pellagrin 164, although,

according to the rules of this study, she would have fallen into the second zone in relation to Pellagrins 91 and 93 at 8 A Street, if her erythema had appeared one day earlier. Another possibly important source of exposure in this case requires mention, although it cannot enter into the statistical calculations. This girl, Pellagrin 114, was a very frequent visitor at the home of her aunt, Pellagrin 163, at 13 F Street from September, 1911, to March 18, 1912, and after March this aunt came to her house at 5 B Street and remained for several days, apparently less than two weeks. The available information in regard to this relationship, therefore, does not permit the classification of Pellagrin 114 in Zone 1. The third and fourth incident cases in Zone 2 were Pellagrins 148 and 149, brothers aged 6 years and 4 years, respectively, living at 15 D Street. These children had lived in this community since birth and at this house since Jan. 1, 1911. Their residence came into the second zone in relation to Pellagrin 160 at 16 C Street from June, 1911, to April, 1912. On Dec. 4, 1911, Pellagrin 145 moved into another adjacent house, 17 D Street, and she continued to live there, so that 15 D Street remained in the second zone in relation to her until its own cases of pellagra developed. In fact, the two little boys, Pellagrins 148 and 149, were intimate playmates of the children at 17 D Street and spent much of their time playing in and about that house. They both developed the initial erythema about July 15, 1912, and, as has been noted in the discussion of Zone 1, their two playmates, Pellagrins 146 and 147, sons of Pellagrin 145 at 17 D Street, developed the disease about Aug. 1, 1912. Here were four little boys, aged 3 to 6 years, living in adjacent houses, in one of which an old pellagrin, mother of two of the children, resided. All four of the children came down with pellagra within an interval of approximately two weeks. All four of these children had had measles at about the same time in May and June, 1912. The fifth case in Zone 2, Pellagrin 280, was a married woman 19 years old. She lived at 13 C Street from July 1, 1911, until April 24, 1912, in next-door relationship to Pellagrin 160 at 16 C Street until April. From May 14, 1912, to June 13, 1912, she lived at 18 D Street, just across the street from Pellagrin 145 at 17 D Street. She then moved to 11 F Street, where her initial erythema appeared in July, 1912, within three months after her exposure at 18 D Street, which has, therefore, been designated as the house of origin of her disease. On the map, Figure 7, she is indicated by a solid circle at 18 D Street and her subsequent residence at 11 F Street is indicated by a hollow circle. She becomes the fifth case originating in the same house with or next door to Pellagrin 145 at 17 D Street, all five of the new pellagrins having the initial attack in July or about Aug. 1, 1912, which is somewhat later than the usual time for the beginning of pel-

lagra in Spartanburg County.[5] These facts suggest a common causative factor for all five of these cases and their residence in proximity to Pellagrin 145 shortly before the development of the disease would appear to challenge attention. The sixth case in Zone 2, Pellagrin 154 at 7 E Street, was a girl 5 years old, who had lived in this house since Nov. 23, 1911, next door to Pellagrin 328 at 9 E Street. The little girl showed her initial erythema early in April, 1912. Her older sister, Pellagrin 153, developed the disease later in 1912, and has been discussed in the group of first-zone cases. The seventh case in Zone 2 was Pellagrin 315, a married woman 20 years old, who lived at 13 F Street from June 18 to Aug. 20, 1912. This house had been vacated by Pellagrin 163 March 18, 1912, and was in next-door relationship to Pellagrin 280 from the onset of her pellagra in July. Aug. 20, 1912, Pellagrin 315 moved to 5 A Street where she developed her initial erythema within a week. She has been designated as incident in the second zone at 13 F Street, where she is indicated on the map, Figure 7, by a solid circle. Her subsequent residence at 5 A Street is indicated by a hollow circle. She left Inman Mills in September, 1912.

The total exposed population in Zone 2 in 1912, according to Table 12, was 587 persons. The seven incident pellagrins in this population give an incidence rate of 1.19 per cent. for this zone in 1912.

There were three cases of pellagra incident in 1912 at Inman Mills in the population living farther away than next door from an active pellagrin for a reasonable period before the disease appeared and, therefore, assigned to Zone 3. At 16 A Street a family in comfortable financial circumstances had resided since November, 1908. Their home at 16 A Street was in the more desirable section of the mill village, close to the superintendent's house, a section in which the older residents, the more efficient and better paid members of the community tended to accumulate, so far as such a tendency was manifest at all at Inman Mills. In this family the father, Pellagrin 152, aged 47 years, and the youngest son, Pellagrin 157, aged 6 years, both developed pellagra about the middle of June, 1912. At the same time, June 15, 1912, Pellagrin 162, a man 78 years old, the father of Pellagrin 152, suffered his initial erythema at his farm about three miles from Inman Mills. The intercourse between these two families was intimate, but the exact date of visits to the farm previous to the development of pellagra were not recorded. Inasmuch as the disease developed in Pellagrins 152 and 157 at nearly the same time, both of them have been assigned to Zone 3. The third case in Zone 3 in 1912 was Pellagrin

5. We hope to present the data in regard to seasonal relationships of pellagra in Spartanburg County in a subsequent paper. The largest number of initial attacks have appeared in the month of June and the largest number of recurrent attacks in the month of May.

150, a girl 16 years old, who came to Inman Mills in March, 1912. From March 13, 1912, to July 19, 1912, she boarded at 15 F Street and then moved with the same family to 5 A Street, where she developed her initial erythema about Aug. 1, 1912. She has been considered incident at 15 F Street, where her residence is indicated by a solid circle on the map, Figure 7, and her residence at 5 A Street has been indicated by a hollow circle. At 15 F Street her residence was next door to 13 F Street in which Pellagrin 163 resided until March 18, 1912. According to the rules of this study, this relationship of only five days cannot be considered. Pellagrin 150 left Inman Mills in September, 1912, and it has not been possible to interview her since that time. She has been assigned to the third zone.

The total population of Zone 3 in 1912, according to Table 12, numbered 687 persons. The three incident pellagrins in this group indicate an incidence rate of 0.44 per cent.

THE DOMICILIARY RELATIONSHIP OF PELLAGRA IN 1913

A general survey of the map for 1913 (Fig. 8) shows a noticeable reduction in the number of incident cases in this year, as compared with 1912, a drop from sixteen to eight. The total number of old pellagrins in the mill, however, has increased from ten in 1912 to twenty-four in 1913. The number of old cases has been increased by the addition of most of the crop of cases incident in 1912. Twelve of these latter pellagrins have remained at Inman Mills, five of them suffering recurrence of symptoms in 1913, while the other seven escaped. There were twelve other pellagrins in whom the disease originated in an earlier year, or elsewhere in 1913. Five of these patients had resided at Inman Mills since 1912 or earlier, four of them suffering recurrence in 1913, while one escaped. The other seven were moved-in cases, five of whom showed active symptoms in 1913. These twenty-four cases have been indicated on the map for 1913, Figure 8, at their respective residences by the hollow circle, or by the hollow square if the disease was inactive in 1913. Several of these pellagrins changed their residences in 1913 and are designated at each house by the respective symbol.

Among the moved-in cases was Pellagrin 1253, who did not show initial symptoms until after her arrival in Inman Mills. She was a married woman, aged 25 years, who moved into 4 E Street on April 23, 1913. Just one week later, on May 1, 1913, her initial erythema appeared, so that she cannot be classed as incident at Inman Mills. Previous to her residence at Inman Mills, Pellagrin 1253 had lived for more than a year in another mill town where pellagra was very prevalent, and it is to this former residence that the origin of her disease has been ascribed. She has been indicated at 4 E Street by a hollow circle on the map for 1913, Figure 8.

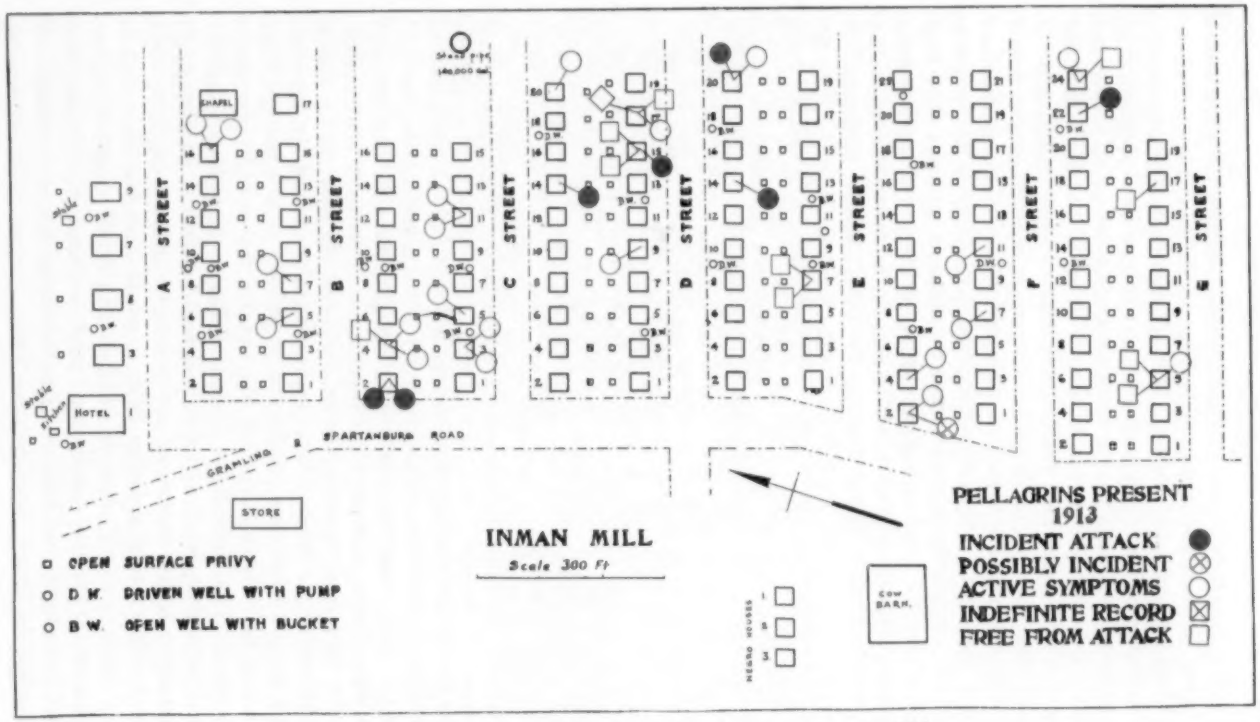

Fig. 8.—Map of Inman Mills, showing pellagrins present in 1913.

The data for the year 1913 are presented in Table 13. The data in regard to the eight pellagrins incident at Inman Mills in 1913 are briefly summarized in Table 7. Two of these new cases appeared in houses in which there was antecedent pellagra, while the remaining six originated in houses next door to antecedent pellagrins. No known cases of pellagra developed in persons living farther away than next door from a pellagrin in 1913. The first case in Zone 1, Pellagrin 588, a married woman aged 28 years, had lived at 15 D Street since Jan. 1, 1911. She was the mother of Pellagrins 148 and 149, the two little boys who contracted the disease in 1912. According to the statements of this woman, she had never had a pellagrous erythema until June, 1913, when the eruption was seen by us. Pellagrin 588 has been designated as incident in Zone 1 in 1913 and she has been indicated at 15 D Street by a solid circle on the map for 1913 (Fig. 8). Pellagrin 587,

TABLE 7.—PELLAGRINS INCIDENT AT DEFINITE HOUSES AT INMAN MILLS IN 1913

House	Residence in House	Zone	Residence in Zone	Onset Date	Pellagrin	Sex	Age
2B	Nov. 1, 1912 - Oct. 22, 1913.....	2	Nov. 1, 1912 - May, 1913....	May, 1913	559	F	24
2B	Since Jan. 11, 1913.....	2	Jan. 11, 1913 - May, 1913....	May, 1913	1059	F	21
14C	Since Dec. 16, 1912.....	2	July, 1912 - June 25, 1913....	June 25, 1913	589	F	32
14D	Mar. 1, 1913 - Apr. 1, 1913.....	2	Mar. 1, 1913 - Mar. 28, 1913..	Mar. 28, 1913	529	M	24
15D	Since Jan. 1, 1911.....	1	Since July 15, 1912.....	June, 1913	588	F	28
20D	Apr. 9, 1913 - June 20, 1913.....	2	Apr. 9, 1913 - May 2, 1913....	May 2, 1913	845	F	50
2E	Since Apr. 23, 1913.....	1	Since Apr. 9, 1913.....	May, 1913	587	F	31
22F	Since Nov. 15, 1911.....	2	Oct. 24, 1912 - June 15, 1913..	June 15, 1913	591	F	26

the second case designated as incident in Zone 1 in 1913, was a married woman 31 years old. She came to 2 E Street, Inman Mills, April 23, 1913. This house was arranged for two families, the other side of it being occupied at the time by Pellagrin 37. In the latter part of May, 1913, while residing in this house, Pellagrin 587 developed a definite erythema on the hands. According to the rules adopted for this study she has, therefore, been designated as incident in this house. When seen by us early in July, 1913, she reported that even before coming to Inman Mills, while at the house of Pellagrin 133 at Mill Village Sa, she had been troubled with sore mouth and diarrhea. Relying on the statements of this woman as to her history in the two or three weeks prior to her arrival in Inman Mills, it would seem justifiable to trace her incidence to the house of Pellagrin 133, where preliminary symptoms were observed. On the other hand, her residence at Inman Mills was in the same zone relationship as the earlier one, since Pellagrin 37 occupied the other side of the same house, and, inasmuch as the initial

erythema seems to have appeared after two weeks of residence here, 2 E Street, Inman Mills, has been designated as the house of origin. This has been done with considerable reservation, and on the map for 1913, Figure 8, this case has been indicated at 2 E Street by a circle containing a cross, because her incidence at this house is regarded as doubtful.

According to Table 13, the total exposed population in Zone 1 in 1913 numbered 118 persons, so that the appearance of two new cases would indicate an incidence rate of 1.69 per cent. for this zone in 1913.

Six of the incident pellagrins have been assigned to Zone 2. Pellagrins 559 and 1059 were two married women, aged 24 and 21 years, respectively, who were living in the same house at 2 B Street when they had initial attacks of pellagra at about the same time. Pellagrin 559 had moved into this house Nov. 1, 1912, coming from 21 F Street. Pellagrin 1059 had boarded at 5 A Street for about three months before moving to 2 B Street on Jan. 11, 1913. Neither had apparently lived near antecedent pellagra before her residence at 2 B Street, which was in next-door relationship to Pellagrin 164 at 4 B Street and to Pellagrins 160 and 161 at 3 C Street. Pellagrin 164 was incident in 1912, but had no recurrence of symptoms in 1913 or in 1914. The residence dates of Pellagrin 160 are rather uncertain for 1913, although it is probable that she spent some weeks in 1913 with her mother, Pellagrin 161, at 3 C Street. Pellagrin 161 is definitely known to have resided at 3 C Street until August, 1913, when she moved to 4 B Street; she suffered a recurrence in 1913. Pellagrins 559 and 1059 both developed the initial erythema at about the same time in May, 1913, and they have been designated as incident in Zone 2 at 2 B Street and are indicated there by solid circles on the map, Figure 8. Pellagrin 559 moved later in 1913 to 11 C Street, where she lived until March, 1914, when the family moved out of town. She has been designated at 11 C Street by a hollow circle on the map for 1913. The third case in Zone 2 was Pellagrin 589, a married woman 32 years old, who had an initial attack during the last week of June, 1913, at 14 C Street. According to the mill records, this family had lived at 13 F Street from May 6 until Dec. 15, 1912. Here they were in second-zone relationship to Pellagrin 280 from July, 1912. At 14 C Street, where they moved Dec. 16, 1912, they were again in the second zone, this time living next door to Pellagrins 148 and 149 and also next door to Pellagrin 588 after June, 1913. Pellagrins 148 and 149 were two little boys who were incident in 1912, but neither of whom showed any symptoms in 1913. Their mother, Pellagrin 588, had a definite attack in May or June, 1913. Pellagrin 589 has, therefore, been designated as incident in Zone 2 at 14 C Street and has been indicated by a solid circle at this house on the map for 1913, Figure 8. The fourth case in Zone 2 was Pellagrin

529, a man aged 24 years, who moved from Spartan Mills to Inman Mills late in February, 1913. He lived at 14 D Street from March 1 until the first of April, 1913. At Spartan Mills he had lived with his family at 175 Jennings Street since January, 1912. From March until May, 1912, Pellagrin 508, who had a severe recurrence in 1912, lived with them. Thereafter, so far as is known, no patient with pellagra resided in their vicinity until they came to 14 D Street March 1, 1913. This house was just across the street from Pellagrins 148 and 149 at 15 D Street. Here Pellagrin 529 developed a severe erythema about March 28, 1913, and he has been designated as incident here in the second zone and indicated by a solid circle at this house on the map, Figure 8. Immediately after the development of pellagra, this man left town with his family, going to the house of his father-in-law at Spartan Mills April 1, 1913. Within two months after his arrival his wife's parents both contracted the disease, the father-in-law dying in the summer of 1913. Pellagrin 529 left Spartan Mills in June, 1913, and went to Tennessee, where he died in September, 1913. The fifth case incident in the second zone in 1913 was Pellagrin 845, a married woman aged 30 years. According to the mill records, this woman lived at 20 D Street with her family from April 9, 1913, until June 20, 1913, when she left town and disappeared from record. Her initial erythema appeared on May 2, 1913, a little more than three weeks after her arrival at Inman Mills. Previous to this residence Pellagrin 845 had lived for nearly a year in another mill village conspicuous for its high incidence of pellagra, but the exact location of her residence there was not ascertained. At 20 D Street she was in next-door relationship to Pellagrins 145, 146 and 147 at 17 D Street. Pellagrin 145 had a recurrence in 1913, but Pellagrins 146 and 147, her two children, did not. Pellagrin 845 has been considered incident in the second zone in Inman Mills at 20 D Street and on the map for 1913, Figure 8, she had been indicated by a solid circle at this house. The sixth case incident in the second zone in this year was Pellagrin 591, a married woman aged 26 years, who had lived at 22 F Street since Nov. 15, 1911. This house had been vacated by Pellagrin 366 just before she moved in Oct. 24, 1912, Pellagrin 636 came to live next door at 24 F Street, remaining there until March 7, 1913. March 20, 1913, Pellagrin 592 moved into this house at 24 F Street. The erythema of Pellagrin 591 appeared about June 15, 1913. She has, therefore, been designated as incident in Zone 2 and has been indicated at 22 F Street by a solid circle on the map for 1913.

According to Table 13, the total exposed population in Zone 2 numbered 636 persons in 1913. The indicated rate of incidence for this zone was, therefore, 0.94 per cent.

There were no cases of pellagra found among the 594 persons living farther away than next door from an antecedent pellagrin in this year. The incidence rate for the third zone in 1913 was, therefore, zero.

THE DOMICILIARY RELATIONSHIP OF PELLAGRA IN 1914

An extensive canvass of Inman Mills was made in 1914, as in the two preceding years. Our field work covered the period from May 1 to Oct. 15, 1914. The data in regard to each house are briefly presented in Table 14. There were at Inman Mills in this year twenty-eight resident pellagrins who were incident in an earlier year, or elsewhere in 1914. Of these, nineteen showed active symptoms in 1914, six escaped recurrence, while for three the record for this year was indefinite. On the map for 1914, Figure 9, the nineteen pellagrins with active symptoms have been indicated at their respective residences by hollow circles. The six pellagrins who escaped recurrence have been designated by hollow squares at their respective residences, while the three cases with indefinite record have been indicated by squares containing a cross. When a pellagrin changed his residence during the year, he has been designated in a similar manner at each house. Among the pellagrins free from recurrence in 1914 were three who had not shown active symptoms for two years. These were Pellagrins 164, 148 and 149, all residents of Inman Mills, who had suffered only the one initial attack in 1912. These three cases appear on the map for 1914, Figure 9, and in Table 14, but have been excluded from consideration as potential centers of infection in 1914.

There were seventeen pellagrins whose incidence in 1914 has been traced to residence at Inman Mills. Seven of these cases appeared in houses in which an antecedent pellagrin had resided for a period of at least two weeks within six months prior to onset, nine arose among persons living next door to an antecedent pellagrin and one case was discovered in a family whose residence at Inman Mills was farther away than next door from an active pellagrin. The seventeen pellagrins incident in definite houses at Inman Mills have been designated at their respective residences on the map, Figure 9, by solid red circles. In several instances a pellagrin incident in one house moved to another house during 1914. Thus, Pellagrin 931, incident at 3 C Street, subsequently resided at 10 B Street, where her mother, Pellagrin 1079, came down with the disease. Later they both moved to 12 D Street and then again back to 3 C Street. Pellagrin 1081, incident at 11 D Street, moved to 4 C Street; Pellagrin 1286, incident at 13 D Street, moved to 3 C Street and Pellagrin 935, incident at 20 D Street, moved across the street to 19 D Street. At these respective subsequent residences each of these pellagrins is designated by a hollow circle on the map. These seventeen incident pellagrins are enumerated in Table 8.

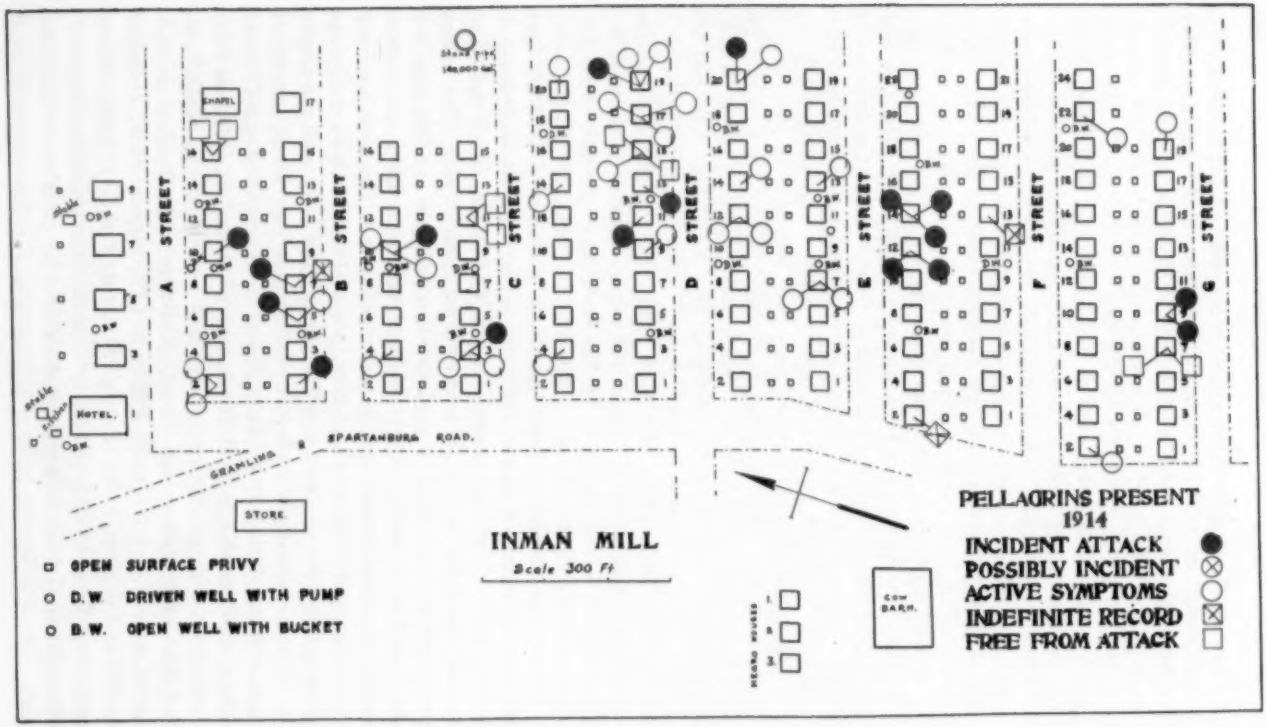

Fig. 9.—Map of Inman Mills, showing pellagrins present in 1914.

Seven cases have been assigned to Zone 1. Pellagrin 1080, a man 40 years old, the father of Pellagrin 114, had lived at 5 B Street since April 24, 1911. His daughter, who was living at home, suffered her initial attack in 1912 with recurrence in 1913 and 1914. Pellagrin 1080 developed his initial erythema in July, 1914. At 7 B Street Pellagrin 1077, a girl 3 years old, had lived with her mother, Pellagrin 883, since Dec. 1, 1913. The mother had her initial attack in 1911, escaped recurrence in 1912, suffered recurrence in 1913 and presented indefinite symptoms without erythema in 1914. The little girl developed her initial erythema about July 15, 1914. The third case in Zone 1, Pellagrin 1079, was a woman 32 years old, whose little daughter, Pellagrin 931, had her initial erythema on May 1, 1914. The family lived at 3 C Street next door to Pellagrin 161 from Aug. 6, 1913, to May 22, 1914. They then moved to 10 B Street, where the mother's initial erythema appeared on June 13, 1914. She has been indicated as incident at 10 B Street, since she resided here for a period of three weeks prior to appearance of the erythema. In July, 1914, this family moved to 12 D Street, remaining there until August 15, when they returned to 3 C Street. The mother, Pellagrin 1079, has been classed as incident in Zone 1. The fourth case in Zone 1, Pellagrin 935, was a boy 6 years old. His family moved to 20 D Street, Inman Mills, late in 1913 and

TABLE 8.—Pellagrins Incident at Definite Houses at Inman Mills in 1914

House	Residence in House	Zone	Residence in Zone	Onset Date	Pellagrin	Sex	Age
10A	Mar. 27 - May 28, 1914.....	2	Mar. 27, 1914 - May, 1914....	May, 1914	1129	M	9
1B	Since Jan. 16, 1910.....	2	June, 1912 - May 4, 1914....	May 4, 1914	930	M	62
5B	Since Apr. 24, 1911.....	1	Since July 1, 1912.....	Late July, 1914	1080	M	40
7B	Since Dec. 1, 1913.....	1	Since Apr., 1911.....	July 15, 1914	1077	F	3
10B	May 23, 1914 - June 27, 1914....	1	Since May 1, 1914.....	June 13, 1914	1079	F	32
3C	Aug. 6, 1913 - May 22, 1914.....	2	Aug. 6, 1913 - May 1, 1914...	May 1, 1914	931	F	7
11D	Nov. 5, 1913 - Feb., 1914.....	2	Apr., 1912 - Feb., 1914.....	May, 1914	1081	F	11
13D	Dec. 12, 1913 - May 22, 1914.....	2	Mar. 16, 1913 - May 15, 1914	May 15, 1914	1286	M	54
19D	Mar. 18, 1914 - July 25, 1914....	1	Since June, 1913.....	Apr., 1914	937	F	9
20D	Dec. 9, 1913 - Mar. 17, 1914.....	1	Since June, 1913.....	Late Mar., 1914	935	M	6
12E	Since Feb. 24, 1914.....	1	Since Apr. 1, 1914.....	Apr. 15, 1914	932	F	9
12E	Since Feb. 24, 1914.....	2	Jan. 15, 1914 - Apr. 1, 1914..	Apr. 1, 1914	933	F	6
14E	Since Feb. 10, 1914.....	2	Jan. 15, 1914 - May, 1914....	May, 1914	1247	M	4
14E	Since Feb. 10, 1914.....	2	Jan. 15, 1914 - May, 1914....	May, 1914	1248	M	6
14E	Since Feb. 10, 1914.....	2	Jan. 15, 1914 - May 15, 1914	May 15, 1914	1249	F	25
9G	Since Jan. 30, 1914.....	2	Jan. 30, 1914 - May 12, 1914	May 12, 1914	938	F	6
9G	Since Jan. 30, 1914.....	1	Since May 12, 1914.....	Late July, 1914	1078	F	42

moved from here to 19 D Street on March 17, 1914. His brother, Pellagrin 936, who was 3 years old, had his initial attack in June, 1913, before coming to Inman Mills, and suffered a recurrence in 1914. In March, 1914, soon after moving to 19 D Street, Pellagrin 935 developed his initial erythema, so that he has been classed as incident at the previous residence, 20 D Street. A few weeks later, in April, 1914, a third case of pellagra appeared in this family, Pellagrin 937, a sister 9 years old. She was the fifth incident case in Zone 1 in 1914, and has been designated as incident at 19 D Street. The sixth incident case in Zone 1, Pellagrin 932, was a girl 9 years old, who developed her initial erythema at 12 E Street April 15, 1914. Her sister, aged 6 years, Pellagrin 933, had suffered her initial erythema on April 1, 1914, so that the interval between the two cases was just two weeks. It is probable that both children acquired the disease at the same time and from the same source, but according to the rules adopted for this study the second case, Pellagrin 932, is classed as incident in Zone 1 in relation to her sister, rather than in Zone 2 in relation to the pellagrins next door to their house, namely, Pellagrins 549, 153 and 154. The two last mentioned were also little girls and playmates of Pellagrins 932 and 933. The seventh incident case in Zone 1 was Pellagrin 1078, a woman 42 years old, who had lived at 9 G Street since Jan. 30, 1914. Her daughter, Pellagrin 938, 6 years old, had developed pellagra May 12, 1914. The mother, Pellagrin 1078, had her first erythema in the last week of July, 1914. She was then in the seventh or eighth month of pregnancy and the attack of pellagra was mild, although she had a definite pellagrous eruption and sore mouth. Inasmuch as she had come to Inman Mills from a pellagrous neighborhood and had been pregnant since before her arrival, it is not improbable that the disease was actually contracted at her previous residence. Under the rules adopted for this study, however, she has been designated as incident in Zone 1 at Inman Mills in 1914.

The total number of exposed persons in Zone 1 in 1914, according to the data of Table 14, amounted to 163. The seven incident pellagrins in this zone indicate an incidence rate of 4.29 per cent. in 1914.

Nine incident pellagrins appeared in the population assigned to Zone 2. Pellagrin 1129, a boy 9 years old, moved to 10 A Street from Mill Village Ap March 27, 1914. He suffered his initial erythema in May, 1914, and the family moved back to their former residence May 28, 1914. This boy has been designated as incident in Zone 2 at 10 A Street. Pellagrin 930, a man 62 years old, had lived at 1 B Street since Jan. 16, 1910. He was not an ordinary factory worker, but held a better paid position of responsibility in the mill. No pellagrins had resided near him until 1912, in which year Pellagrin 164 developed the disease at 4 B Street. In 1913 pellagrins were living in two houses

just across the street from him, at 2 B Street and 4 B Street, and one of these, Pellagrin 161 at 4 B Street, remained during 1914. This man, Pellagrin 930, developed his initial erythema May 4, 1914, accompanied by diarrhea and general weakness. He remained away from his work until June 1. The third case in Zone 2, Pellagrin 931, a girl 7 years old, had lived with her parents at 3 C Street since Aug. 6, 1913. This house had just previously been vacated by Pellagrins 160 and 161, who moved to 4 B Street, immediately behind 3 C Street, where Pellagrin 161 remained during 1914, also. The little girl, Pellagrin 931, developed her initial erythema about May 1, 1914, at 3 C Street. The fourth case in the second zone, Pellagrin 1081, was a girl eleven years old, who had resided at 6 B Street from Nov. 15, 1911, to Aug. 31, 1913. The family then moved to 7 F Street, a house in the third zone, where they remained until Oct. 31, 1913. They then moved to 11 D Street, where they remained until February, 1914. This house was next door to Pellagrin 589 at 14 C Street during this entire period, and to Pellagrin 160 at 14 D Street after Jan. 15, 1914. In February the family moved to 4 C Street, where Pellagrin 1081 developed her initial erythema in May, about three months after the termination of the exposure at 11 D Street. The exact date of the appearance of erythema was not recorded in this case. If it appeared after May 15, the case would be designated as incident at 4 B Street, because Pellagrin 931, another little girl across the street at 3 C Street, had developed her initial erythema May 1, 1914. Although in this study we are adhering strictly to the rules adopted at the outset, it is nevertheless permissible to suggest that the relation of her home at 4 C Street to the very active pellagra focus at 3 C Street should be noted in passing. We have no idea as to how long before the appearance of the initial erythema an individual may be capable of disseminating pellagra, but it is doubtless a somewhat variable period. In this study, of course, no pellagrin is being considered as a possible center of infection until the date of the initial eruption. Pellagrin 1081 has, therefore, been designated as incident at the earlier residence, 11 D Street. The fifth case in Zone 2, Pellagrin 1286, was a man 54 years of age, who had lived next door to pellagrins since March 16, 1913. Dec. 12, 1913, he moved to 13 D Street, where he was next door to Pellagrins 588, 589, 148 and 149 in 1913 and 1914 and to Pellagrin 160, in addition, in 1914. He developed his initial erythema in this house May 15, 1914. A week later he moved to 4 C Street and Aug. 13, 1914, he moved away from Inman Mills. He died of pellagra about July 10, 1915, on a farm five miles from Inman Mills. The sixth case in Zone 2, Pellagrin 933, a girl 6 years old, had lived at 12 E Street since Feb. 24, 1914. Previously, this family resided at 15 E Street. At 12 E Street they were in next-door relationship to Pellagrins 549, 153 and 154. Pellagrins 153

and 154 were little girls, playmates of Pellagrin 933. The initial erythema appeared April 1, 1914, in this case. Pellagrin 932, sister of Pellagrin 933, also developed the erythema here April 15, and she has been discussed above in the group of cases developing in the first zone. The seventh, eighth and ninth cases in Zone 2 all developed at about the same time in May, 1914, at 14 E Street, so that no one of them can be regarded as antecedent to the others. They were Pellagrin 1249, a woman 25 years old, and her two sons, Pellagrins 1247 and 1248, aged 4 and 6 years, respectively. The family had lived at 11 E Street from Sept. 2, 1913, to Feb. 10, 1914, and were there in next-door relationship to Pellagrin 160 at 14 D Street from January 15 to February 10. They then moved to 14 E Street, a house in next-door relationship to Pellagrins 549, 592, 932 and 933. These two little boys played most of the day with the little girls at 12 E Street and at 7 E Street. The two boys and their mother developed the erythema about May 15, that is, four to six weeks after the little girls next door (Pellagrins 932 and 933) had shown the eruption. All three have been designated as incident in the second zone at 14 E Street.

According to Table 14, the total exposed population in Zone 2 numbered 586 persons in 1914. The nine incident cases, therefore, indicate an incidence rate of 1.54 per cent. for this zone in 1914.

One new case of pellagra appeared in a family living farther away than next door from an active pellagrin in 1914. This was Pellagrin 938, a girl 6 years old, who had lived at 9 G Street since Jan. 30, 1914. Next door to this house Pellagrin 164 lived at 7 G Street until March 10, 1914. She has, however, been excluded from consideration as a center of infection in this study in 1914, because she had not suffered an attack of pellagra since 1912. There was no other known case of pellagra in the immediate neighborhood of 9 G Street previous to the appearance of the erythema in Pellagrin 938. This little girl was an intimate playmate of the two little girls at 7 E Street, Pellagrins 153 and 154. Her erythema appeared on May 12, 1914, at about the same time that the other children who played with these girls were attacked by the disease (Pellagrins 932 and 933 at 12 E Street). Another possibility to be considered is that her mother, Pellagrin 1078, who has already been discussed above among the cases in Zone 1, may really have contracted pellagra before the family came to Inman Mills in January, 1914, and that the daughter may have acquired it from her. These are merely conjectures. The fact remains that this case, Pellagrin 938, has been designated as incident in Zone 3, in accordance with the rules adopted for this study.

According to Table 14, the total population in Zone 3 numbered 384 persons in 1914. The one case arising in this zone indicates an incidence rate of 0.26 per cent.

PELLAGRA AT INMAN MILLS SINCE 1914

Since the fall of 1914 we have not visited this mill village, and no complete house-to-house survey of it has been made, so far as we know. We are aware that some investigation was undertaken there in 1915 and in 1916 by the U. S. Public Health Service, and we had the pleasure of furnishing Professor Voegtlin a card index of the cases at Inman Mills on our records at the end of 1914. Exact information in regard to pellagra at Inman Mills in 1915 and 1916 is not at hand, but we know that this community has still continued to be an active focus of pellagra.

During our visits to Spartanburg City in August, 1915, and in August, 1916, complete lists were made of all pellagrins who had applied for treatment at the hospitals of the city, at the Pellagra Hospital of the U. S. Public Health Service and at the Pellagra Hospital provided by Spartanburg County at the County Farm. Our experience has shown that relatively only a small proportion of pellagrins are likely to apply for hospital treatment, especially during the initial attack, because of their reluctance to acknowledge the diagnosis, and inasmuch as Inman Mills is twelve miles from Spartanburg City, not many pellagrins could be expected to come to the city from that village. According to the records of these hospitals, Pellagrin 1403, the mother of Pellagrins 153 and 154, a woman 28 years old, with whom we became well acquainted at Inman Mills during 1912, 1913 and 1914, developed her initial attack of pellagra at 7 E Street in 1915; Pellagrin 1404, aged 5 years, another daughter of Pellagrin 1403, developed her initial attack in this same house in 1916; Pellagrin 1407, a married woman, had her first attack at a house on F Street in May, 1916, and Pellagrin 1435 also had her initial attack at Inman Mills in 1916, the location of her house not having been ascertained. All of these cases came to Spartanburg for treatment. There can be no doubt, therefore, that new cases of pellagra have continued to appear in the population of Inman Mills in the years subsequent to the termination of our epidemiologic study in that community.

COMMENT

The epidemiologic study of pellagra at Inman Mills, presented in the preceding pages, has been conducted under especially favorable circumstances, because this village had been recently built and occupied only since 1902. The records of the families occupying each house during the whole period of existence of the village have made it possible to ascertain the exact houses and the exact dates of occupancy for people who have been met with by us elsewhere in the county. As a result we feel confident that a large proportion, probably a majority,

of all cases of pellagra existing at Inman Mills previous to 1912 have come to our knowledge. Our own house-to-house surveys in 1912, 1913 and 1914 have been exceptionally thorough and complete in this community, and probably only very few recognizable pellagrins have escaped detection here in these years. The community is a more distinctly isolated unit than is Spartan Mills, and this has helped to keep the study simple. Furthermore, the same system of sewage disposal, namely, the open surface privy, continued to be used at Inman Mills throughout the period of our study.

The progressive extension of pellagra in this community seems to us to be a fact which cannot successfully be disputed. The number of pellagrins incident here in each year and the number of other active

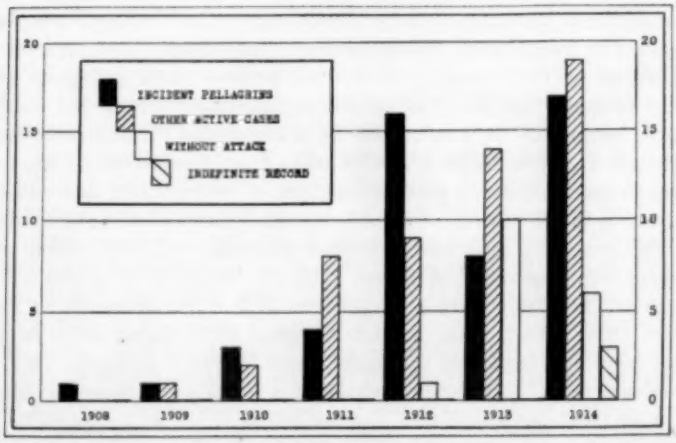

Fig. 10.—The number of pellagrins present in Inman Mills in each year from 1908 to 1914, inclusive. Pellagrins without attack were not observed here until 1912, when one such case was present. In 1914, three pellagrins with indefinite record were present.

pellagrins present are indicated in Table 9 and presented graphically in Figure 10. It is evident that pellagra was not a very prevalent disease at Inman Mills previous to 1911. Even in 1911 only four cases are known to have originated here. This year was one in which Spartanburg County, as a whole, experienced an ernormous increase in pellagra. Our records[6] have shown 234 incident pellagrins in the county in 1911 as compared with 141 in 1910 and 211 in 1912, and at Spartan Mills[1] there were twenty-two recognized incident cases in

6. Siler, J. F., Garrison, P. E., and MacNeal, W. J.: The Incidence of Pellagra in Spartanburg County, S. C., and the Relation of the Initial Attack to Race, Sex and Age, THE ARCHIVES INT. MED., 1916, **18**, 173.

1911, as against fourteen in 1910 and eight in 1912. Inman Mills, being off the main line of travel, evidently escaped to a large extent this increase of incident pellagra in 1911. In the latter part of 1911, however, the effects of the epidemic began to become evident at Inman Mills through the arrival of seven pellagrins, who had contracted the disease elsewhere (Fig. 6). One of these, Pellagrin 726, came to 18 F Street June 29, 1911, and moved away from the village again in September, 1911. Another, Pellagrin 163, came in September, 1911, to 13 F Street. Two others, Pellagrins 91 and 93 moved into 9 F Street in November, 1911, and from there to 8 A Street Dec. 31, 1911, and away from the village again March 27, 1912. A fifth, Pellagrin 145, moved in at 17 D Street in December, 1911, and a sixth, Pellagrin 514, came in December, 1911, to 1 A Street. The seventh, Pellagrin 328, came from Zone 1 in Spartan Mills, where she had manifested pre-

TABLE 9.—INCIDENT PELLAGRINS AND OTHER PELLAGRINS RESIDENT IN INMAN MILLS COMMUNITY IN EACH YEAR TO OCTOBER, 1914

	1908	1909	1910	1911	1912	1913	1914	Sum
Incident pellagrins	1	1	2*	4	16	8	17	80*
Other active pellagrins	0	1	2	8	9	14	19	53
Pellagrins without recurrence	0	0	0	0	1	10	6	17
Pellagrins with uncertain record	0	0	0	0	0	0	3	3
Total active pellagrins	1	2	5*	12	25	22	36	103*
Total pellagrins present	1	2	5*	12	26	32	45	123*

* Including Pellagrins 198 and 882, who developed the initial erythema in 1911 within six months after moving away from Inman Mills and are, therefore, classed as possibly incident at Inman Mills in 1910.

monitory symptoms of pellagra, to 9 E Street on Nov. 16, 1911, developing her initial erythema at 9 E Street early in the spring of 1912. On April 1, 1912, these moved-in pellagrins were occupying the houses at 1 A Street, 17 D Street, 9 E Street and 13 F Street. Reference to the map for 1912, Figure 7, shows that of the sixteen persons who acquired pellagra at Inman Mills in 1912, no less than eleven contracted the disease while living in one of these identical houses or next door to one of them. The remarkable increase in new cases of pellagra at Inman Mills in 1912, following the epidemic in the county generally in 1911, would appear to have been caused largely by the influx of pellagrins into this somewhat segregated community at the end of 1911, whereby were provided four new centers for the spread of the disease, in which foci most of the new cases of 1912 appeared.

In 1913, on the other hand, the disease became distinctly less prevalent at Inman Mills, only eight new cases appearing, while at Spartan

Mills the new cases shot upward to thirty-one. In 1914, when Spartan Mills again improved, having only eighteen incident cases, Inman Mills suffered as severely as in 1912, having seventeen incident pellagrins in this year. When it is recalled that these two industrial communities are situated only twelve miles apart, that they are both engaged in the weaving of cotton cloth, both influenced alike by weather conditions, financial conditions, food conditions and industrial changes, it would appear impossible to explain the contrast which they present in respect to incidence of pellagra in different years by assuming that these variations have been due to variations in general prosperity or in the supply of food. On the other hand, a recognition of the fact that Spartan Mills is situated in the main business center of the county, on the main line of travel, and that Inman Mills is more segregated, off the beaten track, will suggest at once clearcut analogies to the mode of spread of other epidemic diseases.

The number of incident cases of pellagra at Inman Mills from 1908 to 1914, according to Table 9, has been fifty in a mean population of approximately 650 persons. No one will be able successfully to maintain that the causative factors of pellagra have not been operating in this mill village. It is, perhaps, worth while, therefore, to summarize these incident cases according to sex and age at onset of the disease, in order to show how characteristically the men in the age period from 15 to 44 have resisted these causative factors at Inman Mills. Such a summary is presented in Table 10. The three men in

TABLE 10.—Distribution According to Sex and Age of the Fifty Pellagrins Incident at Inman Mills, From 1908 to 1914, Inclusive

Age	0-14	15-29	30-44	Over 45	Age Unknown	Total
Females	9	14	9	1	0	33
Males	9	1	2	5	0	17

the age period 15 to 44 years in this table were Pellagrins 198, 529 and 1080, aged 41, 24 and 40 years, respectively, at the onset of the disease. Pellagrin 198 has also been included in the previous paper in this series as possibly incident at Spartan Mills. He was a chronic alcoholic. Pellagrin 529 said that he used whisky occasionally. The record of Pellagrin 1080 does not show whether he used alcohol or not. The occurrence of only three incident cases of pellagra in men from 15 to 44 years of age in this village during a period of seven years, while eighteen children under the age of 15 years, thirty-three women, aged from 15 to 44, one woman over 45 and five men over 45 years were

attacked by the disease, is quite in accord with the well-known relative insusceptibility of men in the active period of life.

The domiciliary relationship between old pellagrins and the newly incident cases seems to us to be the most significant feature of the pellagra situation at Inman Mills. The actual number of persons in

TABLE 11.—THE INCIDENCE OF PELLAGRA IN THE POPULATION IN EACH OF THE THREE DOMICILIARY ZONES AT INMAN MILLS IN 1912, 1913 AND 1914

Year	Zone 1			Zone 2			Zone 3		
	Exposed Population	Incident Cases	Incidence per Cent.	Exposed Population	Incident Cases	Incidence per Cent.	Exposed Population	Incident Cases	Incidence per Cent.
1912	129	6	4.65	587	7	1.19	687	3	0.44
1913	118	2	1.69	636	6	0.94	594	0	0.00
1914	163	7	4.29	586	9	1.54	384	1	0.26
Sum	410	15	3.66	1809	22	1.22	1665	4	0.24

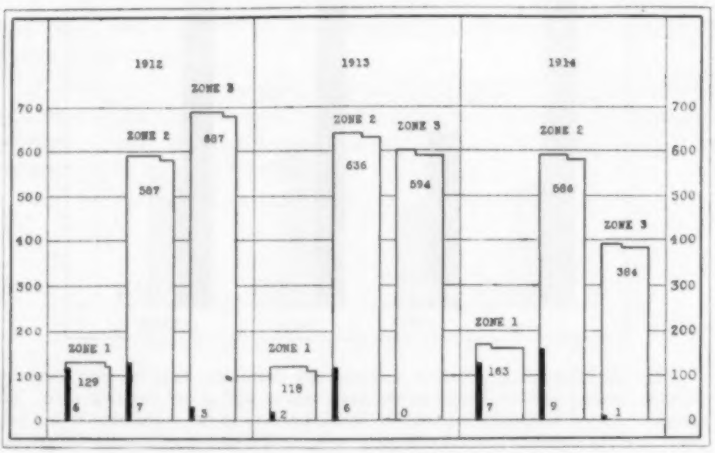

Fig. 11.—The total number of persons who were exposed in each of the three domiciliary zones in 1912, 1913 and 1914 is indicated by the area of the large columns. The included black column indicates in each instance the portion of the respective group which contracted pellagra.

each of the three zones of exposure for 1912, 1913 and 1914 is shown in summarized form in Table 11 and presented graphically in Figure 11. The incidence rates in each zone in each year are shown in Figure 12. During these three years 3.66 per cent. of the persons residing in Zone 1

contracted pellagra, 1.22 per cent. of the persons residing in Zone 2 contracted it and only 0.24 per cent. of the persons residing in Zone 3. In other words, living next door to a pellagrin has been associated with a five-fold increase in the danger of contracting pellagra as compared with living farther away in the same village, and living in the same house with a pellagrin has been associated with a fifteen-fold increase in this danger. A study of the maps accompanying this paper will show that this correlation has not been essentially due to the segregation of the pellagrous population in a particular part of the community,

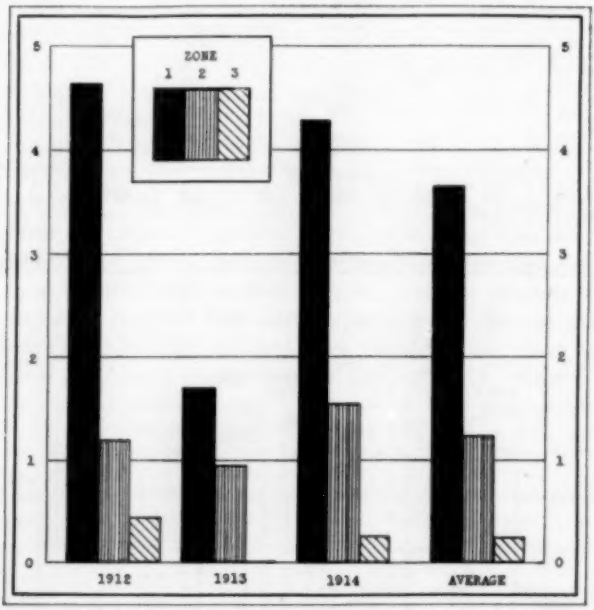

Fig. 12.—The black columns indicate the incidence rate of new cases of pellagra among persons living in the same house with a pre-existing case. The columns striped vertically indicate the incidence rate in the population living next door, and the columns striped obliquely indicate the incidence rate in the population living in the same village but farther away than next door from a pre-existing case of pellagra.

but that in each year there have existed separate distinct foci of pellagra in various parts of this village.

SUMMARY

1. Inman Mills is a cotton mill village of about 650 persons, situated in the country, relatively segregated from the main line of travel in

Spartanburg County. In several respects it presents a contrast to Spartan Mills, approaching more nearly the rural type of community in respect to water supply, sewage disposal, gardening, domestic animals and food supply.

2. This village remained relatively free from pellagra until after the great extension of the disease in Spartanburg County in 1911. In the following year there was a marked increase in the incidence of pellagra at Inman Mills in several very definite small foci, and since 1912 it has remained an active endemic center of the disease.

3. Men between 15 and 44 years of age have very largely escaped the disease here just as they have elsewhere in Spartanburg County.

4. In each of the three years of intensive epidemiologic study, the new cases of pellagra were found to have arisen almost exclusively in persons living in the same house with antecedent pellagrins, or next door to such houses.

5. In this community the spread of pellagra has evidently proceeded from the sick person to his healthy neighbors, either directly or indirectly through very limited distances.

6. Only a small percentage of the neighbors have been attacked in any year, and it is evident that susceptibility has been an important factor in this respect.

7. The relation of the spread of pellagra to the location of domicile at Inman Mills has been essentially the same as at Spartan Mills. These studies support the conclusions of our Second Progress Report in regard to the spread of pellagra.

TABLE 12.—Domicile Relationship—Inman Mills—1912

1912	Zone 1					Zone 2				Zone 3		
House Street and Number	Antecedent Case	First Erythema	Time in Zone 1	Exposed Population		Antecedent Case	Time in Zone 2	Exposed Population		Time in Zone 3	Exposed Population	
				Total	Incident Cases			Total	Incident Cases		Total	Incident Cases
A Street												
1	514	1911	To June 25, 1912..... (Moved June)	5	1	.....	.....	..	..	Aug. - end 1912..... (New families)	32	0
	113	1912	July 14 - Aug., 1912..... (New family; moved Aug.)	7	0							
2	....	....	.....	..	..	113, 514	To Aug., 1912.....	12	0	Aug. - end 1912.....	5	0
3	....	....	.....	..	..	113, 514, 315, 150	To Sept., 1912.....	5	0	Sept. - end 1912.....	6	0
4	....	....	.....	..	..	113, 514, 150, 315, 114, 163	Entire 1912.....	5	0			
5	150	1912	Aug. 1 - Sept., 1912.....	15	0	91, 93	To Mar. 27, 1912..... (Moved Mar.)	10	0	Mar. 27 - Aug. 1, 1912.. (New families)	13	0
	315	1912	Aug. 20 - Sept., 1912							Sept. - end 1912		
6	....	....	.....	..	..	91, 93	To Mar. 27, 1912..... (Moved Mar.)	2	0	Mar. 27 - July, 1912.... (New family)	3	0
						114, 163, 150, 315	July - end 1912.....	2	0			
7	....	....	.....	..	..	91, 93, 315, 150	To Mar. 27, 1912..... Aug.1 - Sept., 1912	6	0	Mar. 27 - Aug. 1, 1912.. Sept. - end 1912	6	0
8	91	1911	To Mar. 27, 1912.....	6	0	114, 163, 150, 315	July - end 1912.....	12	0	Mar. 27 - July, 1912.... (New family)	3	0
	93	1911	(Moved Mar.)									
9	....	....	.....	..	..	152, 157	June - end 1912.....	3	0	To June, 1912.....	3	0
10	....	....	.....	..	..	91, 93, 315, 150	To Mar. 27, 1912..... Aug.1 - Sept., 1912	4	0	Mar. 27 - Aug. 1, 1912.. Sept. - Nov., 1912 (Moved Nov.; no further data)	4	0
12	....	....	.....	..	..	.....	.....	..	..	Entire 1912.....	3	0
14	....	....	.....	..	..	152, 157	June - end 1912.....	2	0	To June, 1912.....	2	0
16	152	1912	June - end 1912.....	5	0	.....	.....	..	..	To June, 1912.....	7	2
	157	1912										
B Street												
1	....	....	.....	..	..	164	June - end 1912.....	4	0	To June, 1912.....	4	0
2	....	....	.....	..	..	160, 161, 164	Apr. - end 1912.....	6	0	To Apr., 1912.....	3	0
3	....	....	.....	..	..	164, 114, 163	June - end 1912.....	3	0	To June, 1912.....	3	0
4	164	1912	June - end 1912.....	5	0	160, 161	Apr. - June, 1912.....	6	1	To Apr., 1912.....	5	0
5	114	1912	July - end 1912.....	7	0	91, 93, 164	To Mar. 27, 1912..... June - July, 1912	8	1			
	163	1909	Summer, 1912									
6	....	....	.....	..	..	160, 161, 164, 114, 163	Apr. - end 1912.....	6	0	To Apr., 1912.....	6	0
7	....	....	.....	..	..	91, 93, 114, 163	Mar. 9 - Mar. 27..... (No data to Mar.) July - end 1912	2	0	Mar. 27 - July, 1912....	2	0
8	....	....	.....	..	..	114, 163	July - end 1912.....	4	0	To July, 1912.....	4	0
9	....	....	.....	..	..	91, 93	To Mar. 27, 1912.....	6	0	Mar. 27 - end 1912.....	6	0
10	....	....	.....	..	..	.....	.....	..	..	Entire 1912.....	14	0

11	....	....	.....	..	..	.....	.....	..	..	Entire 1912.....	6	0
12	....	....	.....	..	..	.....	.....	..	..	Entire 1912.....	7	0
13	....	....	.....	..	..	152, 157	June - end 1912.....	4	0	To June, 1912.....	4	0
14	....	....	.....	..	..	.....	.....	..	..	Entire 1912.....	5	0
15	....	....	.....	..	..	152, 157	June - end 1912.....	7	0	To June, 1912.....	7	0
16	....	....	.....	..	..	.....	.....	..	..	Entire 1912.....	9	0
C Street												
1	....	....	.....	..	..	160, 161, 164	Apr. - end 1912.....	8	0	Mar. 1 - Apr., 1912..... (No data to Mar.)	4	0
2	....	....	.....	..	..	160, 161	Apr. - end 1912.....	11	0	To Apr., 1912.....	11	0
3	160	1911	Apr. 1 - end 1912..... (New family)	5	1	.....	.....	..	..	To Apr., 1912..... (Moved away)	4	0
	161	1912	June - end 1912									
4	....	....	.....	..	..	160, 161	Apr. - end 1912..... (New family)	6	0	To Feb. 29, 1912..... (Moved away)	2	0
5	....	....	.....	..	..	160, 161, 164	Apr. - end 1912.....	4	0	To Apr., 1912.....	4	0
6	....	....	.....	..	..	160, 161	Apr. - end 1912.....	3	0	To Apr., 1912.....	3	0
7	....	....	.....	..	..	.....	.....	..	..	Entire 1912.....	3	0
8	....	....	.....	..	..	.....	.....	..	..	Entire 1912.....	6	0
9	....	....	.....	..	..	.....	.....	..	..	Entire 1912.....	3	0
10	....	....	.....	..	..	.....	.....	..	..	Entire 1912.....	2	0
11	....	....	.....	..	..	.....	.....	..	..	Entire 1912.....	4	0
12	....	....	.....	..	..	.....	.....	..	..	Feb. 20 - end 1912..... (No data to Feb.)	4	0
13	....	....	.....	..	..	.....	.....	..	..	Apr. 23 - end 1912..... (No data to Apr.)	5	0
14	....	....	.....	..	..	160	To Apr., 1912.....	13	0			
						148, 149	June - end 1912					
15	....	....	.....	..	..	160	To Apr., 1912.....	8	0	Apr. - end 1912.....	4	0
16	160	1911	To Mar. 31, 1912..... (Moved Mar. 31; family counted at 3 C for 1912)	..	..	145, 146, 147, 148, 149	Apr. - end 1912..... (New families)	13	0			
18	....	....	.....	..	..	160, 145, 146, 147, 148, 149	Entire 1912.....	4	0			
20	....	....	.....	..	..	145, 146, 147	Entire 1912.....	9	0			
D Street												
1	....	....	.....	..	..	.....	.....	..	..	Entire 1912.....	7	0
2	....	....	.....	..	..	.....	.....	..	..	Entire 1912.....	12	0
3	....	....	.....	..	..	.....	.....	..	..	To Aug. 31, 1912..... (Moved Aug; no further data)	10	0
4	....	....	.....	..	..	.....	.....	..	..	Entire 1912.....	6	0
5	....	....	.....	..	..	.....	.....	..	..	Entire 1912.....	2	0
6	....	....	.....	..	..	153, 154	Apr. - end 1912.....	3	0	To Apr., 1912.....	4	0
7	....	....	.....	..	..	.....	.....	..	..	Entire 1912.....	6	0
8	....	....	.....	..	..	328, 153, 154	Spring - end 1912..... (New family)	6	0	To spring, 1912..... (Moved away)	9	0
9	....	....	.....	..	..	328	May - Nov. 26, 1912...	6	0	To May, 1912..... Nov. - end 1912	6	0
10	....	....	.....	..	..	328, 153, 154	Spring - end 1912.....	15	0	To spring, 1912.....	3	0
11	....	....	.....	..	..	328	May - Nov. 26, 1912...	10	0	To May, 1912.....	10	0

TABLE 12.—Domicile Relationship—Inman Mills—1912—(*Continued*)

1912	Zone 1					Zone 2				Zone 3		
House Street and Number	Antecedent Case	First Erythema	Time in Zone 1	Exposed Population		Antecedent Case	Time in Zone 2	Exposed Population		Time in Zone 3	Exposed Population	
				Total	Incident Cases			Total	Incident Cases		Total	Incident Cases
D St. cont'd												
12	328	1912	May – Nov. 26, 1912..... (New family; counted at 9 E; moved Nov.)	..	..	328	Spring – May, 1912.... (Moved away)	4	0	To spring, 1912.....	4	0
										Nov. 27 – end 1912..... (New family)	3	0
13	....	....	.....	..	..	160, 328, 148, 149	To Apr., 1912..... May – end 1912	7	0			
14	....	....	.....	..	..	328, 148, 149	May – end 1912.....	9	0	To May, 1912.....	9	0
15	148	1912	June – end 1912.....	6	0	145, 160	To June, 1912.....	8	2			
	149	1912										
16	....	....	.....	..	..	145, 146, 147, 148, 149	Entire 1912.....	5	0			
17	145	1904	Entire 1912.....	6	2							
	146	1912	Aug. – end 1912									
	147	1912										
18	....	....	.....	..	..	145, 146, 147, 148, 149	Entire 1912.....	17	1			
19	....	....	.....	..	..	145, 146, 147	Entire 1912.....	12	0			
20	....	....	.....	..	..	145, 146, 147	Entire 1912.....	21	0			
E Street												
1	....	....	.....	..	..	37	Entire 1912.....	27	0			
2	37	1908	Entire 1912.....	17	0							
3	....	....	.....	..	..	.....	.....	..	..	Entire 1912.....	5	0
4	....	....	.....	..	..	37	Entire 1912.....	12	0			
5	....	....	.....	..	..	158, 154	Apr. – end 1912.....	4	0	To Apr., 1912.....	4	0
6	....	....	.....	..	..	.....	.....	..	..	Mar. – Dec., 1912..... (Moved; no further data)	3	0
7	154	1912	Apr. – end 1912.....	4	1	328	Spring – Apr., 1912....	5	1	To spring, 1912.....	5	0
	153	1912	June – end 1912									
8	....	....	.....	..	..	153, 154, 883	Apr. – end 1912.....	5	0	To Apr., 1912.....	5	0
9	328	1912	Spring – May, 1912..... (No data to spring; moved Apr. 30)	4	0	328, 153, 154	May – July 15, 1912... (New families; moved July; no further data)	6	0			
10	....	....	.....	..		328, 153, 154, 280	Spring – July 15, 1912. New family; moved July; no further data)	2	0	To spring, 1912..... (Moved away)	2	0
11	....	....	.....	..	..	328	Spring – Nov. 26, 1912 (New family; moved away)	6	0	To Jan. 31, 1912..... (Moved away)	2	0
										Dec. – end 1912..... (New family)	2	0

12	....	....	.....	..	..	163, 328 153, 154, 280	Entire 1912.....	7	0			
13	....	....	.....	..	..	328	May - Nov. 26, 1912...	10	0	Apr. 12 - May, 1912.... (No data to Apr.) Nov. 26 - end 1912	10	0
14	....	....	.....	..	..	163, 328, 280	To May, 1912..... July - end 1912	6	0			
15	....	....	.....	..	..	.....	.....	..	..	Entire 1912.....	10	0
16	....	....	.....	..	..	163	To Mar. 18, 1912.....	12	0	Mar. 18 - end 1912.....	7	0
17	....	....	.....	..	..	.....	.....	..	..	Entire 1912.....	9	0
18	....	....	.....	..	..	.....	.....	..	..	Entire 1912.....	17	0
19	....	....	.....	..	..	.....	.....	..	..	Entire 1912.....	17	0
20	....	....	.....	..	..	.....	.....	..	..	Entire 1912.....	8	0
22	....	....	.....	..	..	.....	.....	..	..	Entire 1912.....	19	0
F Street												
1	....	....	.....	..	..	37	Entire 1912.....	24	0			
2	....	....	.....	..	..	.....	.....	..	..	Entire 1912.....	9	0
3	....	....	.....	..	..	37	Entire 1912.....	15	0			
4	....	....	.....	..	..	.....	.....	..	..	Entire 1912.....	14	0
5	....	....	.....	..	..	883	Dec. - end 1912.....	10	0	To Dec., 1912.....	8	0
6	....	....	.....	..	..	.....	.....	..	..	Entire 1912.....	19	6
7	883	1911	Dec. 1 - end 1912..... (New family)	13	0	.....	.....	..	..	To Dec., 1912.....	11	0
8	....	....	.....	..	..	883	Dec. - end 1912.....	5	0	To Dec., 1912.....	9	0
9	....	....	.....	..	..	280, 883	July - end 1912.....	20	0	To July, 1912.....	18	0
10	....	....	.....	..	..	883	Dec. - end 1912.....	2	0	To Dec., 1912.....	7	6
11	280	1912	July - end 1912..... (New families)	8	0	168	To Mar. 18, 1912.....	6	0	Mar. 18 - May 25, 1912. (Moved away)	4	0
12	....	....	.....	..	..	280, 883	July - end 1912.....	5	0	To July, 1912.....	5	0
13	163	1909	To Mar. 18, 1912..... (Moved Mar.)	6	1	280	July - end 1912.....	14	1	Apr. - July, 1912..... (New families)	17	6
14	....	....	.....	..	..	163 280	To Mar. 18, 1912..... July - end 1912	18	0	Mar. 18 - July, 1912....	10	0
15	....	....	.....	..	..	163	To Mar. 18, 1912..... (Moved Mar.)	6	0	Mar. 18 - end 1912..... (New fam'lies)	26	1
16	....	....	.....	..	..	163 280	To Mar. 18, 1912..... July - end 1912	9	0	Mar. 18 - July, 1912....	3	0
17	....	....	.....	..	..	.....	.....	..	..	Apr. - end 1912..... (No data to Apr.)	15	0
18	....	....	.....	..	..	163	Jan. 16 - Mar. 18, 1912	11	0	Mar. 18 - Sept. 30, 1912 (Moved; no further data)	10	0
19	....	....	.....	..	..	636	Oct. 24 - end 1912.....	9	0	To Oct. 24, 1912.....	4	0
20	....	....	.....	..	..	.....	.....	..	..	Entire 1912.....	9	0
21	....	....	.....	..	..	636	Oct. 24 - end 1912.....	5	0	To Oct. 24, 1912.....	11	0
22	....	....	.....	..	..	636	Oct. 24 - end 1912.....	5	0	To Oct. 24, 1912.....	5	0
24	636	1911	Oct. 24 - end 1912..... (New family)	10	0	.....	.....	..	..	Feb. - Oct. 24, 1912..... (No data to Feb.)	13	0
Negro houses												
1	....	....	.....	..	..	.....	.....	..	..	Dec. - end 1912..... (No data to Dec.)	9	0
2	....	....	.....	..	..	.....	.....	..	..	Nov. - end 1912..... (No data to Nov.)	4	0
3			(No data for 1912)									

TABLE 13.—Domicile Relationship—Inman Mills—1913

1913	Zone 1					Zone 2				Zone 3		
House Street and Number	Antecedent Case	First Erythema	Time in Zone 1	Exposed Population		Antecedent Case	Time in Zone 2	Exposed Population		Time in Zone 3	Exposed Population	
				Total	Incident Cases			Total	Incident Cases		Total	Incident Cases
A Street												
1	....	....	.....	..	..	.....	.....	..	..	Entire 1913.....	17	0
2	....	....	.....	..	..	.....	.....	..	..	Entire 1913.....	12	0
3	....	....	.....	..	..	.....	.....	..	..	Entire 1913.....	6	0
4	....	....	.....	..	..	114	Entire 1913.....	5	0			
5	....	....	.....	..	..	.....	.....	..	..	Feb. 4 - end 1913..... (No data to Feb.)	6	0
6	....	....	.....	..	..	114, 883	Entire 1913.....	9	0			
7	....	....	.....	..	..	.....	.....	..	..	Entire 1913.....	5	0
8	....	....	.....	..	..	114, 883	Entire 1913.....	8	0			
9	....	....	.....	..	..	152, 157	Entire 1913.....	3	0			
10	....	....	.....	..	..	883	Dec. 1 - end 1913.....	6	0	Jan. 16 - Dec., 1913....	6	0
12	....	....	.....	..	..	.....	.....	..	..	Entire 1913.....	6	0
14	....	....	.....	..	..	152, 157	Entire 1913.....	2	0			
16	152 157	1912 1912	Entire 1913.....	5	0							
B Street												
1	....	....	.....	..	..	160, 161, 164, 559, 1059	Entire 1913.....	4	0			
2	559 1059	1913 1913	May - Oct. 22, 1913..... (Moved Oct.) May - end 1913	6	0	160, 161, 164	To May, 1913.....	5	2			
3	....	....	.....	..	..	114, 160, 161, 164, 1059, 559	Entire 1913.....	3	0			
4	164 161 160	1912 1912 1911	To July 29, 1913..... (Moved July) Aug. 1 - end 1913 (New family; counted at 3 C)	5	0							
5	114	1912	Entire 1913.....	8	0							
6	....	....	.....	..	..	114, 160, 161, 164, 883	Entire 1913.....	12	0			
7	883	1911	Dec. 1 - end 1913..... (New family; counted at 5 C)	..	..	114	To Nov. 29, 1913..... (Moved Nov.)	5	0			
8	....	....	.....	..	..	114, 883	Entire 1913.....	4	0			
9	....	....	.....	..	..	883	Dec. - end 1913.....	6	0	To Dec., 1913.....	6	0
10	....	....	.....	..	..	544, 559, 883	June 30 - July 21, 1913 Oct. 23 - end 1913	8	0	To June 30, 1913.....	8	0
11	....	....	.....	..	..	.....	.....	..	..	Feb. 1 - end 1913..... (No data to Feb.)	5	0
12	....	....	.....	..	..	544, 559	June 30 - July 21, 1913 Oct. 23 - end 1913	7	0	To June 30, 1913.....	7	0

13	....	....	.....	..	..	152, 157	Entire 1913.....	4	0			
14	....	....	.....	..	..	554, 559	June 30 – July 21, 1913 Oct. 23 – end 1913	6	0	To June 30, 1913.....	6	0
15	....	....	.....	..	..	152, 157	Entire 1913.....	6	0			
16	....	....	.....	..	..	.....	.....	..	..	Entire 1913.....	6	0
C Street 1	....	....	.....	..	..	160, 161, 164, 559, 1059	To Oct. 7, 1913..... (Moved Oct.; no further data)	12	0			
2	....	....	.....	..	..	160, 161	Feb. 5 – July 31, 1913.. (No data to Feb.)	13	0	Aug. – end 1913.....	16	0
3	161	1912	To July 31, 1913.....	4	0	160, 161,	Aug. 6 – end 1913.....	8	0			
	160	1911	(Moved July)			164, 559, 1059	(New family)					
4	....	....	.....	..	..	160, 161, 883	To Nov. 30, 1913..... (No further data)	10	0			
5	883	1911	Feb. – Nov. 30, 1913..... (New family; moved Nov.)	8	0	160, 161, 164	To Jan. 30, 1913..... (Moved away)	4	0			
							Dec. – end 1913..... (New family)	6	0			
6	....	....	.....	..	..	160, 161, 883	To Nov. 30, 1913..... (No further data)	3	0			
7	....	....	.....	..	..	.883	Feb. – Nov. 30, 1913... (No further data)	6	0	To Feb., 1913.....	2	0
8	....	....	.....	..	..	280, 883	Feb. – end 1913.....	5	0	To Feb., 1913.....	5	0
9	....	....	.....	..	..	544, 559	June 30 – July 21, 1913 Oct. 23 – end 1913	3	0	To June 30, 1913.....	3	0
10	....	....	.....	..	..	280, 544, 559	Feb. 6 – end 1913.....	9	0	To Feb. 6, 1913.....	3	0
11	544	1910	June 30 – July 21, 1913... (New family; moved July)	7	0	559	July 25 – Oct. 15, 1913. (New family; moved Oct.)	3	0	To June 30, 1913..... (Moved away)	11	0
	559	1913	Oct. 23 – end 1913 (New family; counted at 2 B)									
12	....	....	.....	..	..	280, 580, 544, 559	Feb. 6 – end 1913.....	7	0	To Feb. 6, 1913.....	4	0
13	....	....	.....	..	..	589, 544, 559	June 25 – end 1913..... (New family)	2	0	To June 25, 1913..... (Moved June)	5	0
14	589	1913	June 25 – end 1913.....	10	0	558, 148, 149	To June 25, 1913.....	12	1			
15	....	....	.....	..	..	589	June 25 – end 1913..... (New family)	2	0	To Feb. 13, 1913..... (Moved away)	4	0
16	....	....	.....	..	..	145, 146, 147, 148, 149, 588, 589	Entire 1913.....	13	0			
18	....	....	.....	..	..	145, 146, 147, 148, 149, 588, 37	Entire 1913.....	7	0			
20	37	1908	Dec. 3 – end 1913..... (New family; counted at 2 E)	.	..	145, 146, 147	To Dec. 3, 1913..... (Moved away)	10	0			

TABLE 13.—Domicile Relationship—Inman Mills—1913 —(*Continued*)

1913	Zone 1					Zone 2				Zone 3		
House Street and Number	Antecedent Case	First Erythema	Time in Zone 1	Exposed Population		Antecedent Case	Time in Zone 2	Exposed Population		Time in Zone 3	Exposed Population	
				Total	Incident Cases			Total	Incident Cases		Total	Incident Cases
D Street												
1	....	....	.....	..	..	.....	.....	..	..	Entire 1913.....	7	0
2	....	....	.....	..	..	.....	.....	..	..	Entire 1913.....	12	0
3	....	....	.....	..	..	.....	.....	..	..	Feb. 6 - end 1913..... (No data to Feb.)	3	0
4	....	....	.....	..	..	.....	.....	..	..	Feb. 1 - end 1913..... (No data to Feb.)	4	0
5	....	....	.....	..	..	.....	.....	..	..	Entire 1913.....	2	0
6	....	....	.....	..	..	153, 154	Entire 1913.....	8	0			
7	....	....	.....	..	..	280	Feb. 6 - end 1913.....	6	0	To Feb. 6, 1913.....	6	0
8	....	....	.....	..	..	153, 154, 280	Entire 1913.....	6	0			
9	280	1912	Feb. 6 - end 1913..... (New family)	2	0	.....	.....	..	..	To Feb. 6, 1913..... (Moved Feb.)	6	0
10	....	....	.....	..	..	153, 154, 280	Feb. 16 - end 1913..... (No data to Feb.)	10	0			
11	....	....	.....	..	..	280, 589	Feb. 6 - end 1913..... (No data to Feb.)	11	0			
12	....	....	.....	..	..	280	Feb. 6 - end 1913.....	12	0	To Feb. 6, 1913.....	2	0
13	....	....	.....	..	..	148, 149, 588, 589	Entire 1913.....	10	0			
14	....	....	.....	..	..	148, 149 588	To Mar. 31, 1913..... (Moved away)	13	1			
							July 28 - Aug. 27, 1913 (New family; moved Aug.; no further data)	2	0			
15	148	1912	Entire 1913.....	7	1							
	149	1912										
	588	1913	June - end 1913									
16	....	....	.....	..	..	145, 146, 147, 148, 149, 588	Entire 1913.....	6	0			
17	145	1904	Entire 1913.....	4	0							
	146	1912										
	147	1912										
18	....	....	.....	..	..	145, 146, 147, 148, 149, 588, 845, 936	Entire 1913.....	10	0			
19	....	....	.....	..	..	145, 146, 147, 845, 37,936	Entire 1913.....	12	0			

20	845	1913	May 2 – June 20, 1913.... (Moved June)	1	0	145, 146, 147	To May 2, 1913.....	21	1			
							June 25 – Dec. 9, 1913.. (New families; moved away)	6	0			
	936	1913	Dec. 9 – end 1913..... (New families; family of Case 936 not counted here for 1913)	2	0							
E Street												
1	....	....	.....	..	..	37, 587, 1253	Entire 1913.....	29	0			
2	37	1908	To Dec. 8, 1913..... (Moved Dec.)	12	1							
	587	1913	May – end 1913									
3	....	....	.....	..	..	1253	May 1 – Aug. 26, 1913..	3	0	To May, 1913,..... Aug. – end 1913	10	0
4	1253	1913	May 1 – Aug. 26, 1913.... (New family; moved Aug.)	5	0	37, 587	To May 1, 1913..... Aug. 26 – end 1913	7	0			
5	....	....	.....	..	..	153, 154	Entire 1913.....	4	0			
6	....	....	.....	..	..	883	To Jan. 31, 1913..... (Moved away)	9	0	Feb. 12 – May 1, 1913... (New family)	6	0
7	153	1912	Entire 1913.....	4	0	1253	May 1 – Aug. 26, 1913..	6	0	Aug. 26 – end 1913		
	154	1912										
8	....	....	.....	..	..	153, 154, 883	Entire 1913.....	6	0			
9	....	....	.....	..	..	153, 154	Jan. 28 – end 1913.....	8	0			
10	....	....	.....	..	..	153, 154, 280, 883	Entire 1913.....	4	0			
11	....	....	.....	..	..	.....	.....	..	..	Entire 1913.....	15	0
12	....	....	.....	..	..	153, 154, 280	Entire 1913.....	9	0			
13	....	....	.....	..	..	.....	.....	..	..	Entire 1913.....	24	0
14	....	....	.....	..	..	280	To Feb. 6. 1913..... (Moved Feb.)	2	0	Feb. 18 – July 15, 1913.. (New family; moved July; no further data)	7	0
15	....	....	.....	..	..	.....	.....	..	..	Entire 1913.....	29	0
16	....	....	.....	..	..	.....	.....	..	..	Jan. 8 – Aug. 31, 1913.. (Moved Aug.; no further data)	7	0
17	....	....	.....	..	..	845	May 2 – June 20, 1913..	2	0	To May 2, 1913..... June 20 – Oct. 15, 1913 (Moved Oct.; no further data)	7	0
18	....	....	.....	..	..	.....	.....	..	..	Entire 1913.....	8	0
19	....	....	.....	..	..	845	May 2 – June 20, 1913..	5	0	Mar. 18 – May 2, 1913.. (No data to Mar.) June 20 – July 24, 1913 (Moved away)	5	0
						936	Dec. 9 – end 1913.....	2	0	Oct. 1 – Dec. 9, 1913.... (New family)	2	0

TABLE 13.—Domicile Relationship—Inman Mills—1913 —(*Continued*)

1913	Zone 1					Zone 2				Zone 3		
House Street and Number	Antecedent Case	First Erythema	Time in Zone 1	Exposed Population		Antecedent Case	Time in Zone 2	Exposed Population		Time in Zone 3	Exposed Population	
				Total	Incident Cases			Total	Incident Cases		Total	Incident Cases
E St. cont'd												
20	....	....	.....	..	..	.....	.....	..	..	Entire 1913.....	8	0
22	....	....	.....	..	..	.....	.....	..	..	Entire 1913.....	28	0
F Street												
1	....	....	.....	..	..	37, 587, 1253	Entire 1913.....	10	0			
2	....	....	.....	..	..	.....	.....	..	..	Jan. 29 - Nov. 15, 1913. (Moved Nov.; no further data)	7	0
3	....	....	.....	..	..	37, 587, 1253	Entire 1913.....	23	0			
4	....	....	.....	..	..	.....	.....	..	..	To Oct. 1, 1913..... (No further data)	12	0
5	....	....	.....	..	..	883	To Jan. 21, 1913..... (Moved away)	10	0	Aug. 26 - end 1913.....	9	0
						1253	May 5 - Aug. 26, 1913.. (New family)	5	0			
6	....	....	.....	..	..	565, 566, 567	Oct. 1 - Dec. 9, 1913....	6	0	To Oct. 1, 1913..... Dec. 9 - end 1913	6	0
7	883	1911	To Jan. 21, 1913..... (Moved Jan.; family of Case 883 counted at 5 C)	5	0	.....	.....	..	..	Mar. 16 - end 1913..... (New families)	16	0
8	....	....	.....	..	..	883	To Jan. 21, 1913.....	12	0	Feb. - Oct. 1, 1913.....	8	0
						565, 566, 567	Oct. 1 - Dec. 9, 1913			Dec. 9 - end 1913		
9	....	....	.....	..	..	883, 280	To Feb. 5, 1913.....	9	0	Feb. 6,- end 1913.....	9	0
10	....	....	.....	..	..	883	To Jan. 21, 1913..... (Moved away)	2	0	Mar. 21 - end 1913..... (New family)	4	0
11	280	1912	To Feb. 5, 1913..... (Moved Feb.; family of Case 280 counted at 9 D)	4	0	.....	.....	..	..	Feb. 6 - end 1913..... (New families)	15	0
12	....	....	.....	..	..	280, 883	To Feb. 5, 1913.....	5	0	Feb. 6 - Mar. 21, 1913.. (Moved away)	5	0
										Aug. 26 - end 1913..... (New family)	5	0
13	....	....	.....	..	..	280	To Feb. 5, 1913.....	2	0	Feb. 6 - end 1913.....	9	0
14	....	....	.....	..	..	280	To Feb. 5, 1913.....	10	0	Feb. 6 - end 1913.....	12	0
15	....	....	.....	..	..	.....	.....	..	..	Entire 1913.....	10	0
16	....	....	.....	..	..	280	To Feb. 5, 1913..... (Moved away)	5	0	Feb. 6 - Mar. 8, 1913... (New family; moved Mar.)	2	0
						636	Mar. 8 - May, 1913.... (New family)	3	0	May - end 1913.....	6	0

17	....	....	.....	..	..	591	Nov. 8 - end 1913..... (New families)	8	0	To June, 1913..... (Moved away)	11	0
18	....	....	.....	..	..	.....	.....	..	..	To Mar. 8, 1913..... (Moved Mar.)	11	0
										Sept. 13 - end 1913..... (New family)	5	0
19	....	....	.....	..	..	636	To Mar. 8, 1913.....	14	0			
						592	Mar. 20 - end 1913					
						591						
20	....	....	.....	..	..	636	Mar. 8 - May, 1913....	7	0	To Mar. 8, 1913.....	7	0
						591	June - end 1913					
21	....	....	.....	..	..	636	To Mar. 7, 1913.....	13	0			
						592	Mar. 20 - end 1913					
						591						
22	591	1913	June - end 1913.....	5	0	636	To Mar. 7, 1913.....	6	1			
						592	Mar. 20 - June, 1913					
24	636	1911	To Mar. 7, 1913..... (Moved Mar.; family of Case 636 counted at 17 G)	6	0							
	592	1911	Mar. 20 - end 1913..... (New family)	4	0							
G Street												
1	....	....	.....	..	..	.....	.....	..	..	Feb. 8 - end 1913..... (No data to Feb.)	4	0
3	....	....	.....	..	..	.....	.....	..	..	Feb. 12 - Sept. 15, 1913 (No further data)	19	0
5	565	1911	Oct. 1 - Dec. 9, 1913.....	..	..	.....	.....	..	..	Mar. 26 - Sept. 15, 1913 (No data to Mar.; moved Sept.)	5	0
	566	1911	(New family; not									
	567	1912	counted here for 1913; moved Dec.; no further data)									
7	....	....	.....	..	..	565, 566, 567	Oct. 1 - Dec. 9, 1913....	4	0	Feb. 22 - Oct. 1, 1913... (No data to Feb.)	14	0
										Dec. 9 - end 1913		
9	....	....	.....	..	..	.....	.....	..	..	Feb. 24 - end 1913..... (No data to Feb.)	3	0
11	....	....	.....	..	..	.....	.....	..	..	Feb. 26 - end 1913..... (No data to Feb.)	3	0
13	....	....	.....	..	..	.....	.....	..	..	Feb. 28 - end 1913..... (No data to Feb.)	9	0
15	....	....	.....	..	..	636	Mar. 8 - May, 1913.... (No further data)	5	0			
17	636	1911	Mar. 8 - May, 1913..... (No data to Mar.; moved May)	4	0	.....	.....	..	..	May - end 1913..... (New family)	7	0
19	....	....	.....	..	..	636, 591	Mar. 9 - end 1913..... (No data to Mar.)	9	0			
Negro houses												
1	....	....	.....	..	.	.....	.....	..	..	Entire 1913.....	9	0
2	....	....	.....	..	.	.....	.....	..	..	Entire 1913.....	4	0
3	....	....	(No data for 1913)									

TABLE 14.—Domicile Relationship—Inman Mills—1914

1914	Zone 1					Zone 2				Zone 3		
House Street and Number	Antecedent Case	First Erythema	Time in Zone 1	Exposed Population		Antecedent Case	Time in Zone 2	Exposed Population		Time in Zone 3	Exposed Population	
				Total	Incident Cases			Total	Incident Cases		Total	Incident Cases
A Street												
1	....	....	.....	..	..	1252, 1253	July 24, 1914, to date..	8	0	To July 24, 1914.....	8	0
2	1253	1912	July 24, 1914 to date....	5	0	930	May 4 - July 24, 1914..	4	0	To May 4, 1914.....	8	0
	1252	1914										
3	....	....	.....	..	..	1252, 1253	July 24, 1914, to date..	6	0	To July 24, 1914.....	6	0
4	....	....	.....	..	..	114, 930, 1252, 1253, 1080	Entire 1914 to date....	5	0			
5	....	....	.....	..	..	.....	.....	..	..	Entire 1914 to date....	6	0
6	....	....	.....	..	..	114, 930, 883, 1077	Entire 1914 to date....	7	0			
7	....	....	.....	..	..	1129	May - May 28, 1914....	5	0	To May, 1914.....	5	0
8	....	....	.....	..	..	114, 1080, 883, 1077, 1129	Entire 1914 to date....	8	0	May 28, 1914, to date		
9	....	....	.....	..	..	152, 157	Entire 1914 to date....	3	0			
10	1129	1914	May - May 28, 1914..... (Moved May)	7	0	883, 1077	To May, 1914.....	14	1			
							June 1, 1914, to date.. (New family)	4	0			
12	....	....	.....	..	..	1129	May - May 28, 1914....	4	0	To May, 1914.....	4	0
										May 28, 1914, to date		
14	....	....	.....	..	..							
16	152	1912	Entire 1914 to date.....	6	0	152, 157	Entire 1914 to date....	2	0			
	157	1912										
B Street												
1	930	1914	May 4, 1914, to date.....	4	0	161	To May 4, 1914.....	5	1			
2	....	....	.....	..	..	161, 930, 931, 1079, 1286	Entire 1914 to date....	11	0			
3	....	....	.....	..	..	114, 930, 1080, 161, 1252, 1253	Entire 1914 to date....	3	0			
4	161	1912	Entire 1914 to date.....	5	0							
5	114	1912	Entire 1914 to date.....	8	1							
	1080	1914	July, 1914, to date									
6	....	....	.....	..	..	114, 161, 1080, 883, 1077, 931, 1286, 1079	To Aug. 31, 1914..... (Moved Aug.; no further data)	6	0			
7	883	1911	Entire 1914 to date.....	8	1							
	1077	1914	July, 1914, to date									
8	....	....	.....	..	..	114, 883, 1059, 931, 1077, 1080, 1079	Entire 1914 to date....	4	0			
9	....	....	.....	..	..	883, 931, 1077, 1059, 1079, 1129	Entire 1914 to date....	8	0			
10	1059	1913	To May 20, 1914..... (Moved May)	2	0	883, 1077	July 22, 1914, to date.. (New family)	4	0			
	931	1914	May 23 - June 27, 1914...	..	1*							
	1079	1914	June 13 - June 27, 1914 (New family; counted at 3 C for 1914; moved June)									

11	....	....	.....	..	..	1060, 931, 1079, 1129	To June 27, 1914.....	4	0	June 27, 1914, to date..	4	0
12	....	....	.....	..	..	1059, 931, 559, 1079	To June 27, 1914.....	7	0	June 27, 1914, to date..	7	0
13	....	....	.....	..	..	152, 157	Entire 1914 to date....	4	0			
14	....	....	.....	..	..	559	To Mar. 10, 1914.....	10	0	Mar. 10 - Sept. 1, 1914.. (Moved away; no further data)	4	0
15	....	....	.....	..	..	152, 157	Entire 1914 to date....	6	0			
16	....	....	.....	..	..	.....	.....	..	..	Entire 1914 to date....	9	0
C Street												
1	....	....	.....	..	..	161, 931, 1079, 1081, 1286	Entire 1914 to date....	10	0			
2	....	....	.....	..	..	931, 1081, 1079, 1286	May 1, 1914, to date...	13	0	To May 1, 1914.....	18	0
3	931	1914	May 1 - May 22, 1914.... (Moved May)	7	0	161	To May 1, 1914.....	8	1			
	1286	1914	May 23 - Aug. 13..... (New family; moved Aug.)	6	0							
	931	1914	Aug. 16, 1914, to date									
	1079	1914	(Family counted above)									
4	1081	1914	May, 1914, to date..... (No data to May)	6	0							
5	....	....	.....	..	..	161, 931, 1079, 1081, 1286	Entire 1914 to date....	6	0			
6	....	....	.....	..	..	931, 1079, 1081, 1286	May 1, 1914. to date...	3	0	To May 1, 1914.....	3	0
7	....	....	.....	..	..	1059, 931, 1079	To June 27, 1914.....	9	0	June 27, 1914, to date..	6	0
8	....	....	.....	..	..	280	Entire 1914 to date....	5	0			
9	....	....	.....	..	..	559, 931, 1059, 1079	To June 27, 1914.....	3	0	June 27, 1914, to date..	3	0
10	....	....	.....	..	..	280, 559	Entire 1914 to date....	5	0			
11	559	1913	To Mar. 10, 1914..... (Moved Mar.)	2	0	589, 931, 1059, 1079	Mar. 11 - July 10, 1914 (New family; moved July; no further data)	6	0			
	164†	1912	.....	..	..							
12	....	....	.....	..	..	559, 280, 280	Entire 1914 to date....	3	0			
13	....	....	.....	..	..	559, 589	To June 30, 1914..... (Moved June; no further data)	2	0			
14	589	1913	To Aug. 21, 1914..... (Moved Aug.)	8	0	588	Aug. 31, 1914, to date. (New family)	2	0			
15	....	...	.....	..	..	589	To Aug. 21, 1914.....	3	0			
16	....	....	.....	..	..	589, 588, 145, 146, 147	Entire 1914 to date....	3	0			
18	....	....	.....	..	..	37, 145, 146, 147, 588, 935, 936, 937	Entire 1914 to date....	3	0			
20	37	1908	Entire 1914 to date.....	5	0							

* Indicates Pellagrin 1079, whose initial erythema appeared on June 13, 1914, three weeks after moving into this house. This residence, therefore, has been considered house of origin

† Pellagrins indicated in this manner are not considered centers of distribution in 1914.

TABLE 14.—Domicile Relationship—Inman Mills—1914—(*Continued*)

1914	Zone 1					Zone 2				Zone 3		
House Street and Number	Antecedent Case	First Erythema	Time in Zone 1	Exposed Population		Antecedent Case	Time in Zone 2	Exposed Population		Time in Zone 3	Exposed Population	
				Total	Incident Cases			Total	Incident Cases		Total	Incident Cases
D Street												
1	....	....	.....	..	..	1081	May, 1914, to date....	6	0	To May, 1914.....	6	0
2	....	....	.....	..	..	.....	.....	..	..	Entire 1914 to date....	9	0
3	....	....	.....	..	..	1081	May, 1914, to date....	3	0	To May, 1914.....	3	0
4	....	....	.....	..	..	.....	.....	..	..	To Mar. 10, 1914..... (Moved Mar.; no further data)	4	0
5	....	....	.....	..	..	1081	May, 1914, to date....	2	0	To May, 1914.....	2	0
6	....	....	.....	..	..	153, 154	Entire 1914 to date....	5	0			
7	....	....	.....	..	..	280	Entire 1914 to date....	6	0			
8	....	....	.....	..	..	153, 154, 280	Entire 1914 to date....	9	0			
9	280	1912	To Sept. 15, 1914..... (Moved Sept.)	2	0							
10	....	....	.....	..	..	280, 931, 153, 154, 1079	Entire 1914 to date....	5	0			
11	....	....	.....	..	..	280, 160, 589	To Feb., 1914..... (Moved Feb.)	6	1			
							Feb., 1914, to date.... (New family)	3	0			
12	931 1079	1914 1914	July 29 - Aug. 15, 1914... (New family; moved Aug.; counted at 3 C)	..	..	160, 280, 592	Feb. 16 - June 30, 1914 (No data to Feb.)	3	0			
							Sept. 1 - Sept. 14, 1914 (New family; moved away)	2	0			
13	....	....	.....	..	..	588, 589, 160, 931, 1079	To May 15, 1914..... (Moved away)	7	1			
							May 23, 1914, to date.. (New families)	7	0			
14	160	1911	Jan. 15, 1914, to date....	1	0							
15	148	1912	Entire 1914 to date.....	6	0							
	149	1912										
	588	1913										
16	....	....	.....	..	..	160, 592, 588, 145, 146, 147	Entire 1914 to date....	3	0			
17	145	1904	To June 19, 1914.....	4	0	37, 588, 935, 936, 937	June 24, 1914, to date. (New families)	6	0			
	146	1912	(Moved June)									
	147	1912										
18	....	....	.....	..	..	145, 146, 147, 588, 935, 936, 937	Entire 1914 to date....	7	0			
19	936	1913	Mar. 13 - July 25, 1914...	2	1	37, 145, 146, 147, 936	To Mar. 16, 1914..... (Moved away)	2	0			
	935	1914	Late Mar. - July 25, 1914									
	937	1914	Apr. - July 25, 1914 (New families; family of Cases 935, 936 and 937 counted at 20 D; moved July)				July 29, 1914, to date.. (New family)	2	0			
20	936	1913	To Mar. 17, 1914..... (Moved Mar.)	3	1	145, 146, 147, 935, 936, 937	Mar. 13 - July 25, 1914 (New families)	6	0			

E Street												
1	....	....	.....	..	..	587	Entire 1914 to date....	9	0			
2	587	1913	Entire 1914 to date.....	17	0							
3	....	....	.....	..	..	.....	.....	..	..	Entire 1914 to date....	8	0
4	....	....	.....	..	..	587	Entire 1914 to date....	7	0			
5	....	....	.....	..	..	153, 154	Entire 1914 to date....	4	0			
6	....	....	.....	..	..	.....	.....	..	..	Entire 1914 to date....	16	0
7	153 154	1912 1912	Entire 1914 to date.....	4	0							
8	....	....	.....	..	..	153, 154	Entire 1914 to date....	6	0			
9	....	....	.....	..	..	153, 154, 932, 933, 931, 1079, 1247, 1248, 1249	Entire 1914 to date....	10	0			
10	...	....	.....	..	..	153, 154, 932, 933	Entire 1914 to date....	12	0			
11	....	....	.....	..	..	153, 154, 592, 1247, 1248, 1249	Feb. 12, 1914, to date.. (No data to Feb.)	4	0			
12	932 933	1914 1914	Apr. 1, 1914, to date..... Apr. 15, 1914, to date	6	1	153, 154, 549	To Apr. 1, 1914.....	9	1			
13	592	1911	Apr. 16, 1914, to date... (No data to Apr.)	3	0							
14	1247 1248 1249	1914 1914 1914	May, 1914, to date.....	1	0	549, 592, 932, 933	Feb. 28 – May, 1914.... (New family)	4	3	To Feb. 9, 1914..... (Moved away)	4	0
15	....	....	.....	..	..	160, 592	Mar. 1, 1914, to date.. (No data to Mar.)	4	0			
16	....	....	.....	..	..	592, 549, 1247, 1248, 1249	Feb. 28, 1914, to date.. (No data to Feb.)	7	0			
17	....	....	.....	..	..	936	To Mar. 10, 1914..... (Moved away)	4	0	May 1, 1914, to date... (New families)	7	0
18	....	....	.....	..	..	592	Apr. 16, 1914, to date..	6	0	To Apr. 16, 1914.....	4	0
19	....	....	.....	..	..	936	To Mar. 17, 1914.....	11	0	Mar. 17, 1914, to date..	9	0
20	....	....	.....	..	..	.....	.....	..	..	Entire 1914 to date....	13	0
22	....	....	.....	..	..	.....	.....	..	..	Jan. 20 – Aug. 2, 1914.. (No further data)	18	0
F Street												
1	....	....	.....	..	..	587, 934	Entire 1914 to date....	6	0			
2	934	1914	May 15 – July 24, 1914 .. (New family; moved July)	9	0	.....	.....	..	..	To Feb. 20, 1914..... (Moved away)	2	0
										July 30, 1914, to date.. (New family)	2	0
3	....	....	.....	..	..	587	Entire 1914 to date....	14	0			
4	....	....	.....	..	..	934	May 15 – July 24, 1914 (New family)	9	0	To Mar. 21, 1914..... (Moved Mar.)	10	0
5	...	....	.....	..	..	.....	.....	..	..	Entire 1914 to date....	6	0
6	....	....	.....	..	..	559	Aug. 8, 1914, to date..	6	0	To Aug. 8, 1914.....	6	0
7	....	.. .	.....	..	..	.....	.....	..	..	To Aug. 10, 1914..... (Moved Aug.; no further data)	9	0
8	....	....	.....	..	..	938, 1078, 559	May 12, 1914, to date..	8	0	To May 12, 1914.....	6	0
9	....	....	.....	..	..	932, 933	Apr. 1, 1914, to date...	8	0	To Apr. 1, 1914.....	10	0
10	....	....	.....	..	..	938, 1078, 559	May 12, 1914, to date.. (New family)	10	0	To Jan. 20, 1914..... (Moved away)	4	0
11	....	....	.....	..	..	549, 932, 933, 1247, 1248, 1249	Feb. 28, 1914, to date..	5	0	To Feb. 28, 1914.....	5	0

TABLE 14.—Domicile Relationship—Inman Mills—1914—(*Continued*)

1914	Zone 1					Zone 2				Zone 3		
House Street and Number	Antecedent Case	First Erythema	Time in Zone 1	Exposed Population		Antecedent Case	Time in Zone 2	Exposed Population		Time in Zone 3	Exposed Population	
				Total	Incident Cases			Total	Incident Cases		Total	Incident Cases
F St. cont'd												
12	....	....	.....	..	..	938, 1078	May 12, 1914, to date..	4	0	To May 12, 1914.....	4	0
13	549	1913	Feb. 28 – Aug. 7, 1914 ... (New family; moved Aug.; no further data)	9	0	.....	.....	..	..	To Feb. 15, 1914..... (Moved away)	2	0
14	....	....	.....	..	..	549	Feb. 28 – Aug. 7, 1914..	9	0	To Feb. 28, 1914.....	9	0
15	....	....	.....	..	..	549, 1247, 1248, 1249	Feb. 28 – June 30, 1914 (New families; moved June; no further data)	5	0	To Feb. 28, 1914..... (Moved away)	10	0
16	....	....	.....	..	..	549	Feb. 28 – Aug. 7, 1914..	9	0	To Feb. 28, 1914.....	5	0
17	....	....	.....	..	..	.....	.....	..	..	Mar. 15 – Aug. 31, 1914 (No data to Mar.; moved Aug.; no further data)	3	0
18	....	....	.....	..	..	549, 591	Mar. 10, 1914, to date. (New family)	5	0	To Feb. 28, 1914..... (Moved away)	10	0
19	....	....	.....	..	..	591	To Mar. 6, 1914.....	6	0	Mar. 6, 1914, to date...	6	0
20	....	....	.....	..	..	591	Jan. 19, 1914, to date..	13	0			
21	....	....	.....	..	..	591	To Mar. 6, 1914.....	3	0	Mar. 6, 1914, to date...	5	0
22	591	1913	To Mar. 6, 1914..... (Moved Mar.; family of Case 591 counted at 19 G)	2	0	591 .	Mar. 6, 1914, to date..	5	0			
24	....	....	.....	..	..	591	To Mar. 6, 1914.....	4	0	Mar. 6, 1914, to date...	2	0
G Street												
1	....	....	.....	..	..	934	May 15 – July 24, 1914	4	0	To May 15, 1914.....	4	0
3	....	....	.....	..	..	934	May 15 – July 24, 1914 (No data to May)	6	0			
5	....	....	.....	..	..	559	Aug. 8, 1914, to date..	8	0	To Aug. 8, 1914.....	8	0
7	164	1912	.....	..	..	.....	.....	..	..	To May 12, 1914.....	9	0
	559	1913	Aug. 8, 1914, to date.... (New family; counted at 11 C)			938, 1078	May 12 – July 31, 1914 (Moved July)	7	0	(Family of Case 164 not counted here)		
9	938	1914	May 12, 1914, to date....	7	1	.....	.....	..	..	To May 12, 1914.....	11	1
	1078	1914	July, 1914, to date									
11	....	....	.....	..	..	938, 1078	May 12, 1914, to date.	4	0	To May 12, 1914.....	4	0
13	....	....	.....	..	..	.....	.....	..	..	Entire 1914 to date....	4	0
15	....	....	.....	..	..	.....	.....	..	..	Entire 1914 to date....	5	0
17	....	....	.....	..	..	591	Mar. 7, 1914, to date..	6	0	To Mar. 7, 1914.....	6	0
19	591	1913	Mar. 7, 1914, to date... (New family)	3	0	591	To Mar. 6, 1914..... (Moved Mar.)	9	0			
Negro Houses												
1	....	....	.....	..	..	.....	.....	..	..	Entire 1914 to date....	7	0
2	....	....	.....	..	..	.....	.....	..	..	Entire 1914 to date....	4	0
3	....	....	.....	..	..	.....	.....	..	..	Entire 1914 to date....	12	0

THE ABSORPTION OF PHENOLSULPHONEPHTHALEIN FROM THE SUBARACHNOID SPACE IN DISEASES OF THE CENTRAL NERVOUS SYSTEM *

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Since 1842 various observers, beginning with Magendie, have demonstrated that pigments injected into the subarachnoid space eventually appear in the urine. Dandy and Blackfan[1] were the first to apply this knowledge to the study of pathologic conditions. They showed that phenolsulphonephthalein injected into the subarachnoid space is harmless and appears in the urine in normal infants in from four to ten minutes. Their studies were confined to hydrocephalus in infants and to certain animal experiments. As a result of these observations they were led to conclude that there is an active circulation of the spinal fluid; that it is constantly absorbed; and that absorption takes place directly into the vascular supply of the whole subarachnoid space. So far as we know, no other pathologic studies have been made in this way. Cushing and Weed,[2] using the same dye in connection with their work on the spinal fluid, were convinced that absorption takes place largely by way of the subarachnoid villi into the cerebral sinuses. Motte and Nageotte[3] believe that there may be considerable absorption of the spinal fluid by way of the perineural lymphatics.

The following observations were made to determine, if possible, whether there might be some disturbance in the excretion of phenolsulphonephthalein in diseases of the central nervous system other than hydrocephalus. The method adopted consisted, in brief, of doing a lumbar puncture, injecting 1 c.c. of neutral phenolsulphonephthalein,[1] catheterizing the patient and timing the appearance of the dye in the urine.

Certain practical points were soon evident, both from the standpoint of accuracy in results and in maintaining aseptic conditions. In the first place it was noted that there was a tendency for the dye to be

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1. Dandy and Blackfan: Internal Hydrocephalus. Am. Jour. Dis. Child., 1914, **8**, 406.

2. Cushing and Weed: Studies on the Cerebrospinal Fluid. Jour. Med. Research, 1914, **31**, 1.

3. Nageotte and Riche: Tabes Dorsalis. Manuel d'Histologie Pathologique. Cornil and Ranvier, Ed. 3, 1907.

distributed along the path of the needle after withdrawal, giving ample time for it to be absorbed in considerable concentration from the subcutaneous tissues. This would allow it to appear in the urine in practically all cases in ten minutes or less, and would obscure the actual appearance from the subarachnoid space. To overcome this tendency it was found practicable to withdraw 2 or 3 c.c. of spinal fluid in a sterile syringe to be reinjected following the phenolsulphonephthalein so as to leave only clear spinal fluid in the needle. In order that 1 c.c. of phenolsulphonephthalein should replace exactly 1 c.c. of spinal fluid, the following method was devised. This, while extremely simple, was quite as satisfactory as the complicated apparatus with stop-cocks, etc., devised for lumbar puncture that one may find on the market.

The method consists of a needle and syringe adapter joined by three quarters of an inch of small rubber tubing. The first connects with the puncture needle, the latter exactly fits the Luer syringes. When the needle enters the subarachnoid space the obturator is withdrawn and the connecting piece, held with a clamped artery forceps which closes the rubber tubing, is immediately slipped into place. One can then at his leisure attach the manometer for reading the pressure or can withdraw exact amounts of fluid by gradually opening the clamp. Having read the pressure and withdrawn 1 c.c. of fluid to be discarded and 3 c.c. to be held in reserve, exactly 1 c.c. of the neutral phenolsulphonephthalein is slowly injected followed by the 3 c.c. of fluid previously withdrawn. The time of injection is noted. Before withdrawing the needle the patient's legs are slowly straightened (the lateral position is used) so that the changed tissue planes tend to prevent any escape of fluid and phenolsulphonephthalein. Great care should be taken in withdrawing the fluid not to exert suction, the intradural pressure being allowed to push back the piston of the syringe unassisted. It is also well, before introducing the phenolsulphonephthalein, to dilute it by allowing 2 or 3 c.c. of fluid to enter the syringe and then slowly to inject the whole. Obviously the strictest aseptic precautions must be observed at every step of the procedure.

Following the injection, the patient is catheterized and the urine allowed to drop into a series of test tubes containing small amounts of sodium hydroxid. These are placed in order in a rack and the time of drawing off each is noted. The first tube to show a definite pink color is an indicator of the excretion time. On the following day, provided the phenolsulphonephthalein has disappeared from the urine, 1 c.c. is injected intramuscularly according to the usual technic for kidney function test, and the time of the appearance in the urine noted. Practically, it is rarely necessary to catheterize the patient on this examination, merely having him void at the end of ten minutes, at which time the dye is in most cases present in the urine. This, with careful urine analysis, was done to rule out any delays due to kidney disease.

Quantitative estimations were made in a considerable number of cases, but these were found to vary so greatly as to be of little value. The dye is apparently absorbed very slowly from the subarachnoid space and in many instances may suffer considerable reduction before complete elimination can take place.

Apparently the observations reported by Kendall[4] had not been

4. Kendall: The Fate of Phenolsulphonephthalein When Injected Into the Animal Organism, Jour. Am. Med. Assn., 1917, **68**, 343.

extended to include the cerebrospinal fluid. A series of fluids were therefore tested for their reducing ability. Eighteen different fluids were incubated with measured quantities of phenolsulphonephthalein for varying lengths of time. Some of these showed a reduction of from 10 to 20 per cent., others no reduction whatever. While there are certain features about this reduction (percentage) that have not yet been explained, it is safe to say that the decrease in the recoverable dye is not sufficiently great to interfere with qualitative tests.

The series discussed below consists of fifty-nine individuals who were selected from the neurologic and medical clinics of Stanford University Medical School so as to include a reasonable number of supposedly normal persons (neurologically), the others representing as great a variety as possible of organic central nervous system diseases. The series may be divided into five groups.

Group I includes twelve persons whose symptomatology, physical signs and spinal fluid analyses suggested no organic disease of the central nervous system or disease of the urinary tract. These are shown in the table. It will be observed that this group contains persons ranging in age from 27 to 54 years. While it is probable that old age, especially when associated with considerable arteriosclerosis, tends to prolong the appearance time, still the results in this group may be taken as fairly well representing the normal appearance. The time in this series averages practically nine minutes. In these individuals there is no apparent relationship between age and appearance time, neither can a definite relationship between spinal fluid pressure and appearance time be established.

Group II is definitely pathologic. It includes thirty-one persons having both physical and laboratory evidence of organic central nervous system disease. Of this number thirty were syphilitics, nine having been diagnosed tabes dorsalis, five paresis, one juvenile paresis, eleven cerebrospinal syphilis, one pachymeningitis hypertrophica cervicalis syphilitica, one Erb's spastic paraplegia, one syphilitic amyotrophic lateral sclerosis, one gumma of parietal bone with meningeal involvement. The other case was one of tuberculous meningitis. In this group the appearance time ranged from five to seventy-four minutes. In tabes the appearance time ranged from fifteen to sixty minutes, with one exception it was thirty minutes or over, averaging forty-two minutes. Again, one finds no direct relationship between the length of the appearance time and the age, but in this group the average spinal fluid pressure was definitely increased. The five paretics ranging from eighteen to fifty minutes, with one exception, all ran thirty minutes or over, averaging thirty-eight minutes. In this group there was more of a correspondence between age and appearance time.

TABLE SHOWING ABSORPTION OF PHENOLSULPHONEPHTHALEIN FROM THE SUBARACHNOID SPACE IN VARIOUS—

Group I.—Individuals Having Neither Physical Nor Laboratory Evidence of Organic Disease of the Central Nervous System.

Number	Age	Clinical Diagnosis	Phthalein Appearance Time		Wassermann		Spinal Fluid Analysis				Colloidal Gold Reaction (Lange)
			Intraspinal, Min.	Intramuscular, Min.	Blood	Spinal	Pressure, Mm.	Nonne	Noguchi	Cells	
48128	27	Gastritis	7	Under 10	.....	.....	100	+	.....	1	0000000000
48471	26	Constipation	5	Under 10	.....	.....	170	.....	.....	2	1000000000
48528	39	Normal	10	Under 10	.....	.....	120	.....	.....	1	0000000000
24669	52	Normal	10	Under 10	.....	.....	110	+	+	2	0000000000
46098	24	Mediastinitis	14	Under 10	.....	.....	130	.....	.....	1	0000000000
47225	29	Normal	10	Under 10	.....	.....	150	.....	.....	1	1100000000
16410	50	Broken nose	10	Under 10	.....	.....	130	.....	.....	2	1110000000
46944	57	Manic depressive	5	Under 10	.....	.....	50	.....	.....	2	0000000000
40629	26	Neurasthenia	6	Under 10	.....	.....	100	.....	.....	1	0011000000
48043	41	Epilepsy	4	Under 10	.....	.....	120	.....	.....	1	0000000000
50080	31	Manic depressive	6	Under 10	.....	.....	130	.....	.....	1	0000000000
50043	23	Normal	7	Under 10	.....	.....	150	+	.....	1	0110000000

Group II.—Individuals Having Both Physical and Laboratory Evidence of Organic Central Nervous System Disease

42163	29	Tabes dorsalis	30	6	+++	+++	200	+++	+++	30	1222232000
37034	51	Tabes dorsalis	45	7	+++	+++	220	++	++	11	2233320000
43842	26	Tabes dorsalis	55	5	+++	+++	150	++	+	50	1221100000
44850	37	Tabes dorsalis	15	4	.....	+++	210	++	+	26	1233310000
27433	47	Tabes dorsalis	34	10	+++	+++	250	++	++	74	0122110000
45495	45	Tabes dorsalis	42	7	+++	+++	310	+++	+++	34	2234310000
30882	35	Tabes dorsalis	55	6	.....	+++	165	++	+	44	1332210000
43409	44	Tabes dorsalis	60	10	+++	.....	180	+	+	12	1123320000
26236	40	Tabes dorsalis	40	6	.....	+++	100	+	+	86	1123100000
34057	52	Paresis	32	6	+++	+++	270	+	+	28	1110000000
N.S.H. 1	46	Paresis	43	8	+++	+++	200	+++	+++	22	5555554433
N.S.H. 2	28	Paresis	18	7	+++	+++	190	+++	+++	75	5555554332
N.S.H. 3	40	Paresis	32	7	+++	+++	210	++	++	50	.....
34457	34	Paresis	45	5	+++	+++	200	+++	+++	150	5544400000
48870	10	Juvenile paresis	23	5	+++	+++	140	+++	+++	42	5333200000
26067	25	Cerebrospinal lues	45	7	+++	+++	170	+++	+++	48	3333300000
46220	29	Cerebrospinal lues	25	11	+++	+++	200	+++	+++	160	1223321000
47383	46	Cerebrospinal lues	74	5	++	+++	190	+++	+++	33	2234320000
48709	33	Cerebrospinal lues	26	4	+++	+++	150	+++	++	56	3444430000
48589	44	Cerebrospinal lues	65	6	+++	+++	150	++	+++	45	1112233000

—Groups of Normal Persons and Persons with Disease of the Central Nervous System

Group I.—Individuals Having Neither Physical Nor Laboratory Evidence of Organic Disease of the Central Nervous System.

Urine	Subjective Symptoms	Physical Signs					
		Eyes	Knee Jerk	Ankle Jerk	Bladder	Dysarthria	Ataxia
Trace alb.	Pain in the epigastrium	Normal	Normal	Normal	Normal	None	None
Normal	Nervousness	Normal	Normal	Normal	Normal	None	None
Normal	Worry	Normal	Normal	Normal	Normal	None	None
Normal		Normal	Normal	Normal	Normal	None	None
Normal	Pain in the chest	Normal	Normal	Normal	Normal	None	None
Normal		Normal	Normal	Normal	Normal	None	None
Normal	Headache	Normal	Normal	Normal	Normal	None	None
Normal	Flight of ideas	Normal	Normal	Normal	Normal	None	None
Normal	Palpitations	Normal	Normal	Normal	Normal	None	None
Normal	Epileptic attacks	Normal	Normal	Normal	Normal	None	None
Normal	Depression	Normal	Normal	Normal	Normal	None	None
Normal		Normal	Normal	Normal	Normal	None	None

Group II.—Individuals Having Both Physical and Laboratory Evidence of Organic Central Nervous System Disease

Normal	Gastric crises; pains in the legs	Pupils unequal; fixed to light	Absent	Absent	Normal	None	Present
Normal	Poor vision; pains in the legs	Pupils fixed; optic atrophy	Present	Present	Incontinence	None	Slight
Normal	Poor vision; pains in legs and arms	Pupils unequal; fixed; optic atrophy	Present	Absent	Normal	None	Slight
Normal	Paresthesias in arms and legs	Pupils unequal; fixed	Absent	Absent	Normal	None	Present
Normal	Photophobia; pains in legs; impotency	Pupils unequal; fixed	Present	Present	Normal	Slight	Absent
Normal	Paresthesias; pains in the legs	Pupils unequal; fixed; irregular	Absent	Absent	Dribbling	None	Present
Normal	Pains in legs; severe gastric crises	Pupils sluggish	Absent	Absent	Normal	None	Absent
Normal	Shooting pains in legs; trophic ulcer	Pupils fixed	Present	Present	Normal	None	Slight
Trace alb.	Pains in legs; difficult urination	Pupils sluggish	Absent	Absent	Dribbling	None	Present
Normal	Euphoric; elated; grandiose	Pupils unequal	Exaggerated	Exaggerated	Normal	Slight	Absent
Normal	Euphoric; partially demented	Pupils fixed	Increased	Increased	Normal	Present	Slight
Normal	Euphoric; violence	Pupils unequal; fixed	Increased	Increased	Incontinence	Present	Present
Normal	Demented	Pupils unequal; fixed	Increased	Increased	Incontinence	Present	Present
Normal	Irritability; headaches	Pupils sluggish	Increased	Increased	Incontinence	Present	None
Normal	Spastic paralysis; mental retrogression	Pupils fixed	Increased	Increased	Dribbling	Present	Slight
Normal	Headache; diplopia	Iritis	Increased	Increased	Normal	None	None
Normal	Headache; vertigo; paresthesias	Pupils unequal	Increased	Increased	Normal	None	Present
Normal	Depression; paresthesias	Pupils sluggish	Increased	Increased	Normal	None	None
Normal	Depression; paresthesias; headache	Unequal; sluggish; irregular pupils	Absent	Absent	Normal	None	None
Normal	Vertigo; pains in legs	Normal	Increased	Increased	Dribbling	None	None

TABLE SHOWING ABSORPTION OF PHENOLSULPHONEPHTHALEIN FROM THE SUBARACHNOID SPACE IN VARIOUS—

Group II.—Individuals Having Both Physical and Laboratory Evidence of Organic Central Nervous System Disease.—(Continued)

Number	Age	Clinical Diagnosis	Phthalein Appearance Time		Wassermann		Spinal Fluid Analysis				Colloidal Gold Reaction (Lange)
			Intraspinal, Min.	Intramuscular, Min.	Blood	Spinal	Pressure, Mm.	Nonne	Noguchi	Cells	
48881	44	Cerebrospinal lues	60	6	.....	+++	170	++	++	73	2334210000
43315	31	Cerebrospinal lues	60	14	+++	+++	190	+++	++	31	2223322000
32271	36	Cerebrospinal lues	30	6	+++	+++	160	++	++	21	2355321000
29145	39	Cerebrospinal lues	15	5	.....	+++	150	++	++	175	1122100000
40181	40	Cerebrospinal lues	40	7	+++	+++	200	+++	++	94	2233000000
39068	32	Cerebrospinal lues	36	6	+++	+++	220	+++	+++	32	2233300000
40478	43	Pachymeningitis cervicalis syphilitica	40	11	+++	+++	200	++	++	42	1122331000
31851	22	Erb's spastic paraplegia syphilitica	5	5	+++	+++	200	++	++	3	3332220000
30747	39	Amyotrophic lateral sclerosis, syphilitic	14	5	+++	+++	170	+++	++	15	0112210000
49721	35	Gumma of parietal bone	30	8	+++	.....	150	++	+++	9	0011000000
48183	24	Tuberculous meningitis	55	8	.....	.....	200	+++	+++	90	0000123332

Group III.—Individuals Having Positive Physical Evidence of Organic Nervous Disease but Practically Negative Laboratory Findings

15429	38	Tabes dorsalis	40	5	.....	.....	170	+	+	4	1122100000
10451-12	60	Tabes dorsalis	60	7	.....	.....	190	.....	.....	2	1111100000
46559	32	Tabes dorsalis	22	7	.....	.....	165	+	.....	4	1121000000
13963	50	Tabes dorsalis	70	10	.....	.....	200	+	+	2	.....
42695	37	Tabes dorsalis	18	7	.....	.....	210	.....	.....	4	0011000000

Group IV.—Individuals Having Syphilis but No Physical or Laboratory Evidence of Central Nervous System Involvement

50754	43	Syphilis	20	Under 10	+++	.....	150	.....	.....	1	0000000000
48329	8	Congenital syphilis	10	Under 10	+++	.....	100	.....	.....	0	0000000000
15319-13	40	Syphilis	22	Under 10	+++	.....	160	.....	.....	2	0010000000
48206	35	Syphilis	30	Under 10	+++	.....	150	.....	.....	1	1111000000

Group V.—Individuals Having Physical or Symptomatic Evidence of Central Nervous Disease but Negative Laboratory Findings

41169	45	Brain tumor	55	10	.....	.....	130	.....	.....	1	0100000000
47706	20	Jacksonian epilepsy	30	9	.....	.....	150	.....	.....	0	0000000000
17868	40	Jacksonian epilepsy	40	6	.....	.....	150	.....	.....	4	.....
48965	46	Arteriosclerosis	51	10	.....	.....	170	.....	.....	0	.....
47971	35	Delirium tremens	40	7	.....	.....	200	.....	.....	1	1111100000
47569	50	Arteriosclerosis	60	7	.....	.....	120	.....	.....	1	0000000000
8050	70	Arteriosclerosis	40	9	.....	.....	130	.....	.....	4	0000000000

—Groups of Normal Persons and Persons with Disease of the Central Nervous System—(*Continued*)

Group II.—Individuals Having Both Physical and Laboratory Evidence of Organic Central Nervous System Disease.—(Continued)

Urine	Subjective Symptoms	Physical Signs					
		Eyes	Knee Jerk	Ankle Jerk	Bladder	Dysarthria	Ataxia
Normal	Herpes zoster; headache	Pupils unequal	Normal	Normal	Normal	None	None
Normal	Pains in legs	Pupils fixed	Increased	Increased	Normal	None	None
Few casts	Headaches; excitement	Pupils sluggish	Increased	Increased	Normal	Present	Present
Few casts	Paresis left hand; headache	Optic neuritis	Normal	Normal	Normal	None	None
Normal	Pains in legs; depressed	Pupils sluggish	Absent	Sluggish	Normal	None	Slight
Trace alb.	Dizziness; headache; nausea; visual disturbances	Pupils sluggish; optic neuritis	Unequal	Sluggish	Normal	None	Present
Normal	Pain in neck and arms, with weakness and wasting	Pupils unequal	Normal	Normal	Normal	None	None
Normal	Paralysis of legs	Pupils irregular	Exaggerated	Increased	Dribbling	None	Spastic
Few casts	Paralysis of legs; pain in legs	Pupils irregular	Increased	Increased	Normal	Present	Marked
Normal	Stupor; headache	Pupils unequal and dilated	Sluggish	Sluggish	Normal	None	None
Pus cells	Headache; delirium	Pupils unequal	Increased	Increased	Normal	None	None

Group III.—Individuals Having Positive Physical Evidence of Organic Nervous Disease but Practically Negative Laboratory Findings

Normal	Pains in legs; difficult urination	Pupils sluggish	Absent	Absent	Normal	None	Marked
Normal	Pains in legs; dizziness (Charcot joint)	Pupils sluggish; irregular	Absent	Absent	Dribbling	None	Marked
Normal	Pains in legs; dizziness	Pupils irregular	Absent	Absent	Normal	None	Marked
Normal	Pains in legs; headache, dizziness	Pupils fixed	Absent	Absent	Normal	None	Marked
Normal	Pains in legs; crises	Pupils fixed	Absent	Absent	Normal	None	Marked

Group IV.—Individuals Having Syphilis but No Physical or Laboratory Evidence of Central Nervous System Involvement

Normal	Impotence	Pupils normal	Normal	Normal	Normal	None	None
Normal	Necrosis of nose	Pupils normal	Normal	Normal	Normal	None	None
Normal	Headache and nervousness	Pupils normal	Normal	Normal	Normal	None	None
Normal	Headaches; depression; paresthesias	Pupils normal	Increased	Normal	Normal	None	None

Group V.—Individuals Having Physical or Symptomatic Evidence of Central Nervous Disease but Negative Laboratory Findings

Normal	Headache	Disks pale	Normal	Normal	Normal	None	None
Normal	Convulsions	Normal	Normal	Normal	Normal	None	None
Normal	Convulsions; headache	Normal	Unequal	Unequal	Normal	None	None
Trace alb.	Weakness; headache; blood pressure 240 mm.	Normal	Normal	Normal	Normal	None	None
Normal	Hallucinations	Normal	Normal	Normal	Normal	None	None
Few casts	Nervousness; dizziness; paresthesias	Normal	Normal	Normal	Normal	None	None
Few casts	Aphasia; dizziness; weakness; blood pressure 190 mm.	Normal	Normal	Normal	Normal	None	None

The pressures against were increased. The eleven cases of cerebrospinal syphilis ranged from fifteen to seventy-four minutes, with one exception running twenty-five minutes or over, averaging forty-three minutes. The average age was lower in this group than in the two preceding. The remaining observations ran forty, five, fourteen, thirty and fifty-five minutes, respectively.

It will be observed that all of these persons, with one exception, the patient with Erb's syphilitic spastic paralysis, showed evidence of more or less meningeal inflammation as indicated by pleocytosis, increased globulins, etc. Histologically, also, all of these types of disease are known to exhibit meningeal changes.

In tabes "thickening or cellular infiltration of the spinal meninges, most marked in the posterior portion of the cord," was found present in all of fourteen cases recently studied by Dr. W. F. Schaller,[5] who is of the opinion that "the tabetic degeneration is a radiculitis subsequent to a primary syphilitic meningitis." This accords with the findings of Spiller,[6] Bresowsky[6] and Schröder.[7] Nageotte believes that the posterior column degeneration is due to an inflammatory process of the radicular nerves involving the perineurium and endoneurium and taking the form of a transverse neuritis, that is just mesial to the spinal ganglia. Here the inflammatory process starts along the posterior columns producing at the same time the characteristic thickenings and round cell infiltration of the meninges throughout the posterior spinal region. This author, with Mott, believes that a considerable absorption of spinal fluid takes place normally by way of the perineural lymphatics which, under the conditions mentioned above, would be greatly impeded.

In paresis Kraepelin[8] says:

> It is not uncommon to find pachymeningitis interna and hematoma of the dura, usually a mere delicate film, but sometimes in the form of a thick coat made up of several layers or of an extensive fresh extravasation of blood, generally on the vertex. One also frequently sees more or less widespread superficial hemorrhages. The pia is always more or less cloudy and thickened, sometimes excessively, especially along the vessels. Microscopic examination shows an increase in the connective tissue and localized infiltrations with lymphocytes and plasma cells. . . . These alterations are generally most apparent over the anterior and middle portions of the hemisphere convexities, also on the inner surface, but less prominent on the basal surface and entirely lacking over the occipital lobes. . . . The veins are greatly distended and

5. Schaller: Early Diagnosis of Tabes Dorsalis, Jour. Am. Med. Assn., 1917, **68,** 190.

6. Spiller: Pathology of Tabetic Ocular Palsy, Jour. Nerv. and Men. Dis., 1915, **42,** 15.

7. Schröder: Ein Beitrag zur Histopathologie der Tabes Dorsalis. Zentralbl. f. Nervenh. u. Psychiat., New Series, 1906, **17,** 585.

8. Kraepelin: General Paresis. Nervous and Mental Disease Monographs, No. 4.

often show thickened walls. The Pacchionian granulations are frequently over developed. In the spinal cord one observes occasional pachymeningitis and frequent leptomeningitis more marked over the dorsal columns. . . . Fürstner is inclined to believe that the spinal cord is affected without exception in paresis. The alterations were most severe in the lumbar and dorsal cord and gradually diminished as they were followed upward. Alzheimer and others have demonstrated infiltration of the vessels with lymphocytes and plasma cells, both in the pia and in the cord itself.

Barker[9] says: "The pathologic basis of cerebrospinal syphilis consists of a syphilitic infiltration and gumma formation that affects the vascular system and the meninges and the white and gray matter of the brain and cord." Spiller thinks that in all these forms of syphilitic disease the process is not limited, but is an involvement of the whole cerebrospinal tract, being only more pronounced in certain areas in the different clinical types.

The widespread vascular and meningeal involvement in these three clinical forms of disease may account for the small degree of difference in their average appearance time. As before noted, these averages were forty-two, thirty-six, and forty-three minutes, respectively. The widest range was in cerebrospinal syphilis, fifteen to seventy-four minutes.

Pachymeningitis cervicalis hypertrophica syphilitica is by definition a meningeal disease. Whether the delay in this instance was due to changes in the absorbing power of the meninges of the cord, or whether it was due to blocking of the circulation to cerebral absorbing areas, is not certain.

As indicated in the table the case of amyotrophic lateral sclerosis showed definite evidence of syphilis of the central nervous system with meningeal involvement. Spiller[10] cites two cases which were "typical clinically and pathologically of amyotrophic lateral sclerosis," and which showed round cell infiltration in the pia typical of syphilitic disease in addition to the usual systemic degeneration. This meningeal infiltration, though probably not extensive, would perhaps account for the very slight delay in the phenolsulphonephthalein excretion. On the other hand, the patient with Erb's paraplegia, with no signs of meningeal inflammation in the fluid, gave a normal excretion time.

The patient with gumma of the parietal bone, while listed separately, might have been included among those with cerebrospinal syphilis, having evidence of meningeal inflammation in the pleocytosis and increased globulin and albumin.

The case of tuberculous meningitis, the only nonsyphilitic disease in this group, came to necropsy and showed very extensive thickening and edema of the meninges of both the brain and cord.

9. Barker: Monographic Medicine, 1916, **4**, 549.
10. Spiller: Syphilis as a Cause of Systemic Degeneration of the Motor Tract. Jour. Nerv. and Ment. Dis., 1912, **39**, 584.

Group III.—This group consists of five clinical tabetics who differ from the foregoing only in the meager pathologic findings in the spinal fluid, all having negative Wassermann, Nonne and Noguchi reactions, cell counts (four or less), and practically negative colloidal gold reactions. Three of these were negative when first observed; two had been thoroughly treated and were negative at the time of these observations. It will be noted, however, that the average excretion time was forty minutes, only two minutes less than that of the tabetics in the foregoing group. This suggests one possibility of a diagnostic significance for this method.

Group IV.—This group represents four syphilitics with no laboratory or physical evidence of central nervous system disease. Their average was twenty-one minutes, or somewhat more than twice that found in the normal controls. The value of this procedure in detecting early involvement of the central nervous system will be further considered in a subsequent communication.

Group V.—This is a mixed series of seven persons having definite physical or symptomatic evidence of organic disease of the central nervous system, but with negative spinal fluids. None of these were syphilitics. The average appearance time was forty-five minutes. There was no definite correspondence to age, nor were the spinal fluid pressures definitely increased. The group represents one brain tumor, two cases of jacksonian epilepsy, three of advanced arteriosclerosis and one of delirium tremens. It is conceivable that in these individuals more or less extensive involvement of the vascular or lymphatic apparatus might exist. This, though not actively inflammatory giving rise to pleocytosis and increase in globulins, might account for the delayed excretion.

In attempting to explain these delays in more than a general way one is met by several difficulties. If one presupposes a limited area of absorbing tissue, the cerebral arachnoid villi for example, a uniform damage to this area would have to be assumed, or that some obstruction to the free flow of the phenolsulphonephthalein to this area must exist. In some such way the wide range of results in persons having the same type of disease, cerebrospinal syphilis, for example, might be explained. Until more necropsies are secured no more definite information as to the method of excretion of the phenolsulphonephthalein can be given by this procedure. It would seem, however, that inflammations involving the meninges with consequent vascular and lymphatic changes cause a delayed excretion of the dye. Even in those instances in which the symptomatology would suggest a localized lesion, the delay in the appearance time would raise the question of a generalized involvement of the meninges.

SUMMARY

1. Phenolsulphonephthalein when injected into the subarachnoid space in normal persons appears in the urine in ten minutes or less.

2. Diseases of the central nervous system, especially when involving the meninges, produce a lengthening of the appearance time to as much as seventy minutes in some cases.

3. This delay cannot be accounted for by disease of the kidneys, or by the reduction of the phenolsulphonephthalein in the spinal fluid.

4. Advanced general arteriosclerosis may be a factor in causing the delay in some instances.

5. In syphilis a lengthening of the appearance time may be produced before any other evidence of central nervous system involvement has appeared.

6. The method may prove of value in detecting instances of organic central nervous system disease in which the ordinary spinal fluid findings are negative or incomplete.

7. At this time no definite conclusion can be drawn as to the exact location of the absorbing tissues.

It is a pleasure to acknowledge our indebtedness to Drs. W. F. Schaller, A. W. Hewlett and A. W. Hoisholt for material and for valuable suggestions. Also to Miss Beatrice Howett and Mr. R. W. Wilcox for technical assistance.

A STUDY OF THE ERYTHROCYTES IN A CASE OF SEVERE ANEMIA WITH ELONGATED AND SICKLE-SHAPED RED BLOOD CORPUSCLES *

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I. INTRODUCTION

The present data relates to the blood corpuscles of a mulatto woman who entered the Washington University Hospital, St. Louis, Nov. 3, 1914. The unusual character of the blood picture at once attracted attention and became the subject of extended study by several members of the hospital staff. The clinical data need not be elaborated, as the history of the case up to June, 1915, has been fully recorded by Drs. J. E. Cook and J. Meyer.[1]

The patient, aged 21, entered the hospital with an ulcer on the leg. The ulcer healed under treatment and after her discharge from the hospital, Dec. 3, 1914, the patient gained in weight and showed general improvement. An ulcer had appeared on the leg at two previous times in her history, the first at the age of 5, and the second at the age of 19. In both instances, with treatment, it soon healed. The third appearance occurred ten month previous to the patient's entering the hospital. Aside from this ulceration the physical examination otherwise furnished apparently little data of evident significance. Examinations for syphilis or parasites were negative. The blood picture constituted the most striking feature of the case and has been more or less persistent up to date, a period of over two and one-half years.

The unusual structural characteristics of the blood corpuscles, together with two apparently similar cases described by J. B. Herrick,[2] and R. E. Washburn[3] seems, as stated by Drs. Cook and Meyer, to justify the conclusion that "we have in these three cases a group which belongs quite apart from anything heretofore described."

My own observations were begun with the purpose of making a detailed study of the peculiar types of red blood corpuscles occurring in this blood and to ascertain if possible their mode of origin and the

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1. Cook, J. E., and Meyer, J.: Severe Anemia with Remarkable Elongated and Sickle-Shaped Red Blood Cells and Chronic Leg Ulcer, THE ARCHIVES INT. MED., 1915, **16**, 644.

2. Herrick, J. B.: Peculiar Elongated and Sickle-Shaped Red Blood Corpuscles in a Case of Severe Anemia, THE ARCHIVES INT. MED., 1910, **6**, 517.

3. Washburn, R. E.: Peculiar Elongated and Sickle-Shaped Red Blood Corpuscles in a Case of Severe Anemia, Virginia Med. Semi-Month., 1911, **15**, 490.

factors involved. The blood was studied in fresh hanging drops, stained preparations and under experimental conditions. The observations on the patient were continued at various intervals during the year following her discharge from the hospital, that is, up to Jan. 1, 1916. Certain aspects of the experimental study as originally planned remain incomplete, but as the work was unavoidably interrupted at the latter date, it has appeared desirable to record at the present time the results so far attained. The work was begun at the Washington University Medical School and completed at the University of Illinois, College of Medicine. The author is indebted to Dr. George Dock of the Department of Internal Medicine of the Washington University Medical School for the opportunities placed at his disposal, and to Dr. C. S. Williamson of the University of Illinois for access to ward patients at the Cook County Hospital. I wish also to express my appreciation of the material assistance, including the use of loan preparations from Herrick's and Washburn's cases, received through the kindness of Drs. Cook and Meyer.

II. GENERAL CYTOLOGIC CHARACTERISTICS OF THE ERYTHROCYTES

The present account relates to conditions in the blood as observed from December, 1914, to June, 1915. Certain changes which occurred in the latter part of the year 1915 will be subsequently noted. Figure 1, made from a stained blood preparation taken in December, 1914, illustrates some of the general structural characteristics of the red blood corpuscles. Instead of presenting the typical rounded disk form, about one-third of the corpuscles are greatly elongated in shape. A large percentage of the latter have a rounded, rod-like shape with more or less tapering ends, and as a rule present a curved or crescentic form (Fig. 1). These crescentic or sickle-shaped elements as observed in stained preparations are homogeneous in structure, and as a rule take, if anything, a darker hemoglobin stain than the disk-shaped corpuscles.

In addition to this remarkable deviation in form the erythrocytes also differ considerably in size. The smaller cells generally take a deeper hemoglobin stain, the lighter or more transparent central area typical of the biconcave disk is usually lacking and the corpuscle is apparently homogeneous in structure and density throughout. Some of the erythrocytes are paler than others and are apparently correctly described as polychromatophilic. Certain other structural variations will be subsequently described. "The red cells varied in number between 1,800,000 and 3,100,000, usually about 2,500,000" (Cook and Meyer,[1] pp. 647-650). It was also determined by Dr. Cook that in blood collected in an isotonic solution to which sodium citrate had been added, and treated against a hypotonic solution, the resistance of the

red cells did not differ materially from normal conditions. Hemolysis was slight at 0.53, marked at 0.29 and complete at 0.25. Nucleated red cells occurred in all preparations. In most cases the nuclei presented the small compact or pyknotic condition of the more highly differentiated normoblast. In some of the smaller sized and less differentiated nucleated corpuscles the nuclei were larger and had the open chromatin network of the younger erythroblast. It is of interest to note that not infrequently there is to be observed a rim of cytoplasm immediately surrounding the nucleus which takes a deeper cytoplasmic stain than the more peripheral part of the cytoplasm, as suggestive of structural differences between the nuclear and cytoplasmic poles of the differentiated erythroblast, in a manner comparable to conditions apparently occurring in the erythroblasts of the embryonic circulation.[4] Erythroblasts were also observed in which the cytoplasmic pole presented the appearance of having already assumed a biconcave disk shape previous to the formation of the nonnucleated red corpuscle or erythroplastid (Fig. 3). Interest attaches to this fact as furnishing further evidence that the assumption of the disk or cup form of the erythrocyte is not necessarily dependent on the extrusion of the nucleus, as has been maintained by several investigators (Emmel[4] pp. 136, 143). It is perhaps to be taken into account that the assumption of this disk shape may possibly be more precocious in this blood than is normally the case for the adult.

Punctate basophilia is not of infrequent occurrence in the nucleated red cells. This cytoplasmic condition was, however, never observed in either the disk-shaped or sickle-shaped nonnucleated erythrocytes. Sickle-shaped corpuscles containing nuclei were not observed. Jolly bodies or Cabot rings were not found. It is of interest to note that there was evidence of phagocytic ingestion of erythrocytes in the peripheral circulation. The cells in which these erythrocytic inclusions were found were apparently of the large lymphocytic or mononuclear type. Certain observations concerning the blood platelets will be described in a separate article.[5]

III. ORIGIN OF THE SICKLE-SHAPED ERYTHROCYTIC ELEMENTS

One of the first questions to present itself concerning these remarkable sickle-shaped erythrocytes relates to their source of origin and mode of formation. In the adult organism the chief source of the non-

4. Emmel, V. E.: Concerning Certain Cytologic Characteristics of the Erythroblasts in the Pig Embryo and the Origin of Nonnucleated Erythrocytes by a Process of Cytoplasmic Constriction, Am. Jour. Anat., 1914, **16**, 127, 141, 147, 148.

5. Emmel, V. E.: Observations Regarding the Erythrocytic Origin of Blood Platelets, in press, Jour. Med. Research, 1917.

nucleated red corpuscles is found in the red bone marrow. Do these elongated forms arise in situ in the same blood-forming organ as an abnormal or end-phase in the cytomorphosis of the erythroblast, or may the nonnucleated element develop as a typical biconcave disk or cup-shaped corpuscle in the bone marrow and undergo further transformation after their passage into the general systemic circulation? Furthermore, in either case how does this transformation take place? With reference to these questions the following data have been derived from stained and fresh blood preparations. In the first instance it may be observed that the fact that none of the sickle-shaped forms were found to contain nuclei, in itself indicates that the assumption of the sickle-shaped form primarily takes place subsequent to the formation of the nonnucleated erythrocyte or erythroplastid from the erythroblast. If this occurs in the circulating blood one would expect to find various stages of the process in the peripheral circulation.

As already indicated, about two-thirds of the circulating red blood corpuscles present a more or less typical biconcave disk shape. At the other extreme are the striking sickle-shaped forms. On closer study, however, it became evident that stages apparently transitional in character could be found between these two types. This is illustrated in Figure 2, in which *a* represents a typical biconcave disk-shaped red corpuscles; *e* and *f* corpuscles possessing two blunt processes situated at opposite margins of the disk; *g* and *h* present the appearance of half disks and *i-k* are intermediate in form between *g* or *h* and the sickle-shaped elements *l-o*. These various forms strongly indicate that the transformation of the red disks into the sickle-shaped elements is taking place in the circulating blood — a conclusion which appears definitely substantiated by the behavior of the erythrocytes in culture preparations.

In a further study of these stages certain interesting structural characteristics are to be observed. In the first place, while there is a gradual increase in the length of the long axis from corpuscles *l-o* in Figure 2, the actual length of the circumference of the arc of the sickle-shaped elements instead of being longer is approximately equal, or, if anything, less than that of the normal disk-shaped erythrocytes. Second, certain structural differences are to be noted between the sickle-shaped elements and the intermediate forms. While the former have a more or less evenly rounded or rod-like contour, corpuscles like *g* still present a flattened disk-like shape. This can be clearly demonstrated by manipulation of the fresh blood under a cover glass in such a way as to rotate the corpuscle while under observation. This is illustrated in Figures 13 and 16, representing camera lucida drawings of two views of the same corpuscle. In each case *a* represents a side view and *b* a profile view of the same corpuscle. Again in *g*, *h*

and *i* and the same is true for Figures 14 and 15, a convex periphery of the more or less crescentic elements takes a deeper hemoglobin stain and presents the form of a thickened rib-like border. In contrast to this the opposite or concave margin of the corpuscle is very thin and relatively more transparent. In *j* and *k* this thin margin has practically disappeared, but there still remains a decided bulging at the center of the crescent, giving it something of a spindle-shaped form. Finally, there is to be noted a form which is evidently correctly interpreted as intermediate between the normal erythrocytic disk and the crescentic forms. This is illustrated in *b*, *c* and *d* in Figure 2, and also in Figures 8 and 9, in which the concavity of the corpuscle instead of being centrally placed is eccentric in position. Consequently the erythrocyte presents a thin flattened region at one side while the remainder of the corpuscle assumes a thickened crescentic form.

These structural characteristics are suggestive as to the manner in which the original disk-shaped erythrocytes may be transformed into the sickle-shaped elements. There is a substantial and growing body of facts indicating that the mature erythrocyte is surrounded by a membrane consisting in part at least of such lipoid substances as lecithin and cholesterin and that the surface tension associated with the membrane of this composition is of such a character as to be an important factor in the production of the flattened biconcave form of the erythrocyte. (Compare also Emmel,[4] pp. 144, 145.) In the normal erythrocyte this depression or concavity is centrally situated and the periphery of the disk has the form of a thickened ring. In the present blood the erythrocytes have evidently undergone structural changes of such a nature that the concavity of the corpuscle may become displaced toward one side of the erythrocyte. Accordingly, the contents of the erythrocytic disk becomes rearranged in the form of a thickened broad crescent, the extremities of which are united by the much thinner membranous part of the corpuscle. The various stages shown in Figures 2, 8, 9 and 10 suggest that this thinner margin gradually retracts, the thickened crescent becomes more rounded and rod-like, and with the wider separation of its ends assumes the sickle-shaped form found in the circulating blood. What appear to be identical transition stages between disk-shaped and sickle-shaped erythrocytes were also present in the blood preparations from Herrick's (Figs. 8-10) and Washburn's cases.

IV. BEHAVIOR OF THE ERYTHROCYTES UNDER EXPERIMENTAL CONDITIONS

(*a*). *Cultures from the Patient's Blood.*—If the preceding conclusion is correct, that the transformation of the erythrocyte into the sickle-shaped form is taking place in the circulating blood rather than

being necessarily confined to the blood-forming organs, it becomes of interest to ascertain the changes which may occur in cultures of the fresh blood. For this purpose culture preparations were made under sterile conditions. A ring of petrolatum was drawn on a carefully cleaned glass slide. A clean sterile cover glass was then brought in contact with a drop of fresh blood and the cover glass quickly placed on the slide in such a way as to bring the drop of blood to the center of the vaselin ring. The edges of the cover glass were also sealed with sterile petrolatum, so as to form an air-tight chamber similar to that used for tissue culture purposes. These preparations were kept at room temperature and observed at two- or three-hour intervals. Within a few hours such preparations show a marked increase in the elongated type of cells. Great numbers and in some cases the majority of the previously apparently normal disk-shaped erythrocytes become transformed into elliptical spindle-shaped and sickle-shaped elements. A prominent feature in the cultures as compared with the freshly drawn blood is the extension of the tips of the spindle-shaped and crescent-shaped forms into long, tapering, hair-like processes (Figs. 11 and 14). The great abundance of these structures make a striking picture when viewed microscopically. It was thought at first that these needle or hair-like processes were merely fibrous threads arising through clotting; but the cells were found to be freely movable in the plasma and were not attached or held in any fixed position by a fibrous network. By careful manipulation of the cover glass by means of pressure with a needle point, the corpuscles could be turned over and viewed from all sides. During such manipulation each corpuscle maintained a fixed form. Although the erythrocytes in this blood can be observed to be abnormally soft and pliable, no success was obtained in bringing about a mechanical transformation of a disk-shaped corpuscle into a sickle-shaped form.

In a further study of the conditions under which these changes occurred in the cultures the following points may be noted. Alterations in form as the result of overheating is eliminated, since the preparations were kept at room temperature. The processes in question can be clearly recognized as in direct continuity with the cytoplasm of the red corpuscle, and in the majority of cases are evidently not to be confused with fibrin formations. Some of the preparations were kept for eight or more days without any further evident changes in the structure or contour of the sickle-shaped elements. It was suggested that the petrolatum used in sealing the preparations by coming into contact with the blood might be a factor in the result, but it was found that the same transformations could be obtained in paraffin-sealed cultures. It may be noted that the elongation of the erythrocyte and the formation of the attenuated processes was not as marked in a free

hanging drop as in the preparations in which the culture drop was in contact with the two adjacent surfaces of the cover glass and slide, but no adequate explanation for this difference was suggested. Since the hanging drop is of course not in contact with the petrolatum sealing the preparation, some attention was given to this point, but as already indicated, the petrolatum is not a factor in the transformations. The matter was also further tested by bringing a small cover glass (about 12 mm. in diameter) into contact with the underside of the culture drop where it would be held in position by capillary attraction. One edge of this disk had also been slightly thickened or bent by heating in order to prevent a compression of the enclosed blood corpuscles. In such preparations the erythrocytic changes were abundant. No conclusive data were obtained from a few preparations kept in both moist and dry chambers. The possibility was also considered as to whether the phenomenon could be placed in the category of crenation processes. This was suggested by the fact that in some cases erythrocytes were observed which had assumed many-pointed, star-shaped forms (compare Fig. 24) representing, probably, abnormal cases of crenation, due no doubt, to the changed structure of the erythrocyte. This possibility, however, appears eliminated through the fact that the erythrocytes undergo the same sickle-shaped changes in preparations in which there was but little, if any, evidence of crenation to be found. Occasionally the sickle-shaped corpuscles themselves manifest the small surface projections typical of crenation.

Most of the above observations were made on blood obtained in January, 1915. At that time and during the next few months the blood picture was comparable to Figure 1. As already indicated, the patient had been discharged from the hospital early in December, 1914, showing general physical improvement. During the latter part of the summer of 1915, however, in consequence of a reappearance of the leg ulcer and a general weakened condition, the patient returned to the hospital. On making an examination of the blood in the ensuing September, I was surprised to find an almost entire absence of the sickle-shaped erythrocytes (Fig. 17). It was only after careful examination that an occasional elongated erythrocyte could be found in a stained preparation. Otherwise the red corpuscles presented a practically normal picture, and in a casual observation could readily be classified as representing normal conditions, at least so far as the erythrocytes were concerned. The contrast is strikingly shown in a comparison of Figures 16 and 1. This result was verified by repeated observations on blood taken at different times. During the next three months (that is, up to Jan. 1, 1916, when the present observations were terminated) the red blood corpuscles continued to present practically the same appearance. Aside from the fact that during this period a positive

Wassermann reaction was obtained (whereas earlier tests had been negative) nothing conclusive was ascertained which would account for this disappearance of the sickle-shaped forms from the circulation. On subsequent inquiry I learned that the sickle-shaped erythrocytes gradually reappeared in the patient's blood.[6]

The interesting question naturally at once arose as to the behavior of the red cells under experimental conditions as compared with the results obtained in January, 1915. For this purpose sterile petrolatum sealed cultures were made as in the former case and kept at room temperature. The result was indeed striking. Within one hour a large number of the erythrocytes had assumed beautiful crescentic and sickle-shaped forms (Figs. 18 and 19). Within six hours the sickle-shaped forms were present in great abundance, and in twenty-four hours in some of the preparations almost all of the erythrocytes had undergone a similar transformation. There was very little if any evidence of crenation. The experiment was repeated several times, but always with the same result. Some of the preparations were kept for eight days or longer, and great numbers of these elongated and sickle-shaped erythrocytic elements were persistent throughout this time. The evidence appears conclusive that even though for some unknown reason the circulatory erythrocytes had temporarily returned to an apparently more normal structure, they still retained the potentiality for transformation into the sickle-shaped forms.

(*b*) *Comparison with Erythrocytes from Normal Blood and from Cases of Anemia, Chlorosis and Leukemia.*—In considering the preceding results, the question arises, is this behavior of the erythrocytes specific for this case or type of blood disease, or may the same reaction be obtained from other blood? In the endeavor to answer this question, culture cases of anemia and chlorosis were obtained at the Barnes Hospital, St. Louis, and also cases of pernicious anemia and myelogenous leukemia at the Cook County Hospital, Chicago. The preparations were made in identically the same manner as in the previous experiments and kept at room temperature. In the case of the normal blood, in some instances the blood drop was placed under the same coverglass with a drop of blood containing the sickle-shaped corpuscles, the two specimens of course not being allowed to come in contact with each other. Figures 11 and 12 are drawings from such a preparation kept at room temperature for five days. The erythrocytes in the nor-

6. For this information I am indebted to Dr. Cook for a personal letter in April, 1916, in which he also expresses the opinion that the positive Wassermann had nothing to do with the blood picture, and says that "in all probability she acquired her lues recently, for she returned to her husband between the time of her first and second stay in the hospital, and she knew that he suffered from venereal disease. There is, moreover, no reason to distrust the first Wassermann reactions."

mal blood (Fig. 12), aside from a slight crenation in some of the corpuscles, manifested no further changes as compared with the elongated sickle-shaped forms (Fig. 11). In the cultures made from the cases of anemia, chlorosis, and myelogenous leukemia the erythrocytes in no instance presented form changes comparable to that of the sickle-shaped erythrocytes.

On the basis of the present experiments, therefore, it appears that the erythrocytic changes observed in the culture preparations are specific for the case of anemia with sickle-shaped corpuscles. It will be of great interest to ascertain to what extent this conclusion will prove true in further experiments on both pathologic blood and other cases of sickle-shaped corpuscles which may be subsequently discovered.

(*c*) *Cultures from the Blood of the Patient's Father.*—In connection with the present subject there is to be described an interesting exception to the foregoing results. This occurred in the case of cultures made from blood of the patient's father. Fresh and stained blood from the father appeared quite normal (Fig. 20). The erythrocytes uniformly presented the typical biconcave disk-shaped form. In January, 1915, culture preparations were made and kept at room temperature. When examined at the end of twenty-four hours, some of the erythrocytes were found to have assumed elongated and sickle-shaped forms (Figs. 21, 22 and 23). The tips of some of the crescents were drawn out into slender tapering processes (Fig. 22). These elongated forms were by no means as abundant as in the patient's blood, but otherwise they appeared entirely comparable to the forms found in her blood. When the next opportunity occurred to see the father again, nearly a year later, his blood still presented an apparently normal condition, but in the culture preparations the erythrocytes again manifested the same tendency toward a transformation into elongated and sickle-shaped forms.

On obtaining this experimental result with the father's blood, a further study was made of stained preparations to ascertain whether any other hematologic features common to both father and daughter could be discovered. The father, a mulatto, aged 54, was apparently in normal health. An analysis of his blood gave 4,500,000 red cells, 11,100 white cells and 86 per cent. hemoglobin (compare Cook and Meyer, Footnote 1, p. 648). The absence of elongated or sickle-shaped red cells in the father's blood has already been indicated. On the other hand, there is to be noted a frequent occurrence of nuclear excrescences in the neutrophils in both cases, as illustrated in Figures 4, 5 and 6. The apparent association of such leukocytic forms with

certain diseases, Gruner,[7] is suggestive of abnormal conditions in the father's blood. Similar excrescences were not observed in the eosinophils. Some of the mononuclear cells in the father's blood contained phagocytic inclusions, but that they were erythrocytic in nature could not be established with certainty. In general, it may be noted that the father's blood is in many respects comparable to the condition of the patient's blood in December, 1915, at which time the sickle-shaped form had practically disappeared from the circulation. With reference to other members of the same family, it may be stated that there were three other children all of whom died at an early age. The mother died of breast cancer. It is of interest to note that all the children suffered from severe anemia (compare also Cook and Meyer[1]).

(*d*) *Effect of Patient's Serum on Erythrocytes from Other Individuals.*—The conclusion that a transformation of normal erythrocytes to sickle-shaped forms is taking place in the peripheral circulation directs attention to chemical or other characteristics of the blood plasma as possible factors productive of these cytologic changes. While this phase of the study remains incomplete, certain results may, however, be recorded with reference to the effect of the patient's serum on erythrocytes taken from the blood of other individuals. With this in view, blood was removed from the patient under aseptic conditions, allowed to clot, centrifuged, and the supernatant serum removed for experimental purposes. Using this serum as a medium, two series of cultures were made comparable to the preparations described in the preceding experiments. To one of these series, normal blood from a healthy individual had been added, and to the other blood taken from a case of pernicious anemia. Observations were made at various times during the next three or four days with the following results. In the case of the normal blood the erythrocytes became softer and more pliable and showed a tendency to adhere to each other. In the case of the anemic blood, however, the erythrocytes were not only adherent in cords and masses, but quite a number of them eventually presented more or less elongated and crescentic forms with pointed tapering processes comparable to those observed in the patient's blood. In a second experiment cultures were made in which the patient's erythrocytes were placed in serum derived from normal blood. Crescentic forms with tapering, hair-like processes developed just as in the cultures from the patient's blood, but were much less numerous (Fig. 16). Evidently transformation of the patient's erythrocytes will continue to a limited extent even in normal serum. A possible criticism which here suggests itself is that in the case of the first experiment the cen-

7. Gruner, O. C.: A Study of the Changes Met With in the Leukocytes in Certain Cases of Malignant Disease, British Jour. Surg., 1915, **3**, 506.

trifuged serum might still have retained a few of the patient's corpuscles and thus account for the forms found in the cultures of anemic blood. While no microscopic examination of the serum was made, there is no reason to suspect that it contained erythrocytic elements from the patient. In the first place, crescentic forms were not observed in the cultures when first made, and second, if such erythrocytic elements were present it would have been expected that crescentic forms would have appeared in the cultures made from normal blood.

In conclusion, it is perhaps not irrelevant to direct attention to certain general aspects of the present phenomenon. The investigations of the pathologist not infrequently bring home the fact that what are designated as abnormal or pathologic processes are frequently, after all, in their fundamental character primarily either inhibitions or accentuations of normal properties of tissue cells. The erythrocyte, in contrast to the majority of static, nonameboid tissue cells, is an isolated, free-floating element, the form of which is determined, not by its mechanical relations to adjacent tissue structures, but by an interaction with the chemical elements of a fluid, the blood plasma. In this medium the erythrocyte, as is well known, tends to assume a flattened form, an obvious advantage of which consists in the presentation of a greater surface for oxidation. This tendency in the differentiation of the erythrocyte finds its most striking expression in the biconcave disk-shaped corpuscle of mammals (compare also Emmel,[4] p. 136).

With reference to our present subject, the suggestion arises that the transformation into crescentic or sickle-shaped forms may be due, in part, at least, to the abnormal or accentuated activity of the same factors which, in the normal hematogenesis of vertebrates, have led to the transformation of the original spherical red blood corpuscle into the biconcave disk-shaped erythrocyte of the adult mammal. In the case of the present patient, the reaction between the erythrocyte and the presumably altered blood plasma is such that the incidence of the factors producing the concavity of the corpuscle is no longer rigidly confined to the center of the disk, with the result that the thinned portion of the corpuscle may shift to one side and the hemoglobin content accumulate in a crescentic configuration at the opposite side of the erythrocytic disk. In consequence of the abnormally softened character of the erythrocytic membrane in anemic blood, the attenuated peripheral margin of such a disk gives way or retracts from the horns of the crescent and there remains the crescentic or sickle-shaped erythrocytic element.

While the present sickle-shaped forms occurred under pathologic conditions, it is interesting to note that apparently similar forms have

been described by Gulliver[8] in the blood of the Mexican deer and Persian deer, where the blood, aside from the usual disks, contained quite a number of less regular forms, some of which he describes as "curved and gibbous in the middle, and acutely pointed at the ends, with a concave and convex margin, like a crescent."

V. SUMMARY

1. General erythrocytic characteristics.

(*a*). About one third of the erythrocytes instead of presenting the normal disk-form are greatly elongated in shape. A large percentage of the latter have a crescentic or sickle-shaped form.

(*b*). Nucleated erythrocytes occurred in all preparations. Some of the normoblasts present a biconcave disk-shape. Punctate basophilia occurs in many of the nucleated red corpuscles, but was not observed in either the disk-shaped or sickle-shaped nonnucleated corpuscles. Jolly bodies or Cabot rings were not found.

(*c*). Phagocytosis of erythrocytes is taking place to a certain extent in the peripheral circulation.

2. Origin of the sickle-shaped forms.

Evidence was advanced indicating that the circulatory erythrocytes undergo structural changes of such a nature that the central concavity of the normal disk becomes displaced to one side and the hemoglobin content accumulates in a crescentic form at the opposite side of the erythrocytic disk. That the thin margin of this disk retracts, the crescentic part becomes more rod-like and with the wider separation of its ends assumes the sickle-shaped forms under consideration, instead of the poikilocytes usually encountered in anemic blood.

3. Behavior of the erythrocytes under experimental conditions.

(*a*). In culture preparations kept at room temperature it was found that great numbers of the previously disk-shaped corpuscles became transformed into elongated and crescentic elements. The tips of the latter were frequently extended into tapering hair-like processes.

(*b*). During one period of the study, for some unknown reason, the abnormal crescentic forms had temporarily disappeared from the circulation. In culture preparations, however, the erythrocytes still manifested the tendency to assume elongated and crescentic forms.

(*c*). Similar cultures from normal blood and from cases of pernicious anemia, chlorosis and myelogenous leukemia gave only negative results.

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8. Gulliver: Proc. Royal Soc. London, 1842, p. 199.

(*d*) An interesting exception was obtained in the case of the patient's father. In this instance the circulatory erythrocytes presented an apparently normal structure, but under culture conditions occasional corpuscles were found to assume elongated and crescentic forms.

(*e*). In culture preparations made by placing erythrocytes from a case of pernicious anemia in the centrifuged serum of the patient's blood, some of the red corpuscles assumed characteristics comparable to those observed in cultures of the patient's blood.

4. In conclusion, it may be stated: (*a*) that the culture reaction of the erythrocytes appears to be specific for this case of anemia, and (*b*) that the manner in which the red blood corpuscles are transformed into the sickle-shaped elements suggests that the phenomenon is in part at least due to an accentuated or abnormal activity of the same factors which in normal hematogenesis are involved in the transformation of the original spherical erythrocyte into a biconcave disk-shaped form.

PLATE I

Fig. 1.—From a stained preparation of the patient's blood made in December, 1914.

Fig. 2.—Drawings from the same preparations as in Figure 1, to illustrate the various types of erythrocytic elements apparently intermediate between the normal biconcave disks (*a*) and the sickle-shaped forms (*o*).

Fig. 3.—A nucleated erythrocyte in which the hemoglobin containing cytoplasm has assumed a biconcave or possibly cup-shaped form previous to its differentiation into a nonnucleated element. From the same source as Figures 1 and 2.

Figs. 4, 5, and 6.—Neutrophils showing nuclear excrescences. Figures 4 and 5 from the patient's blood in January and December, 1915, respectively. Figure 6 from the patient's father, December, 1915.

Fig. 7.—Phagocytosis of erythrocytes (*2*) in the peripheral circulation.

Figs. 8, 9 and 10.—Erythrocytes from Herrick's case of severe anemia with sickle-shaped red blood corpuscles.

PLATE I

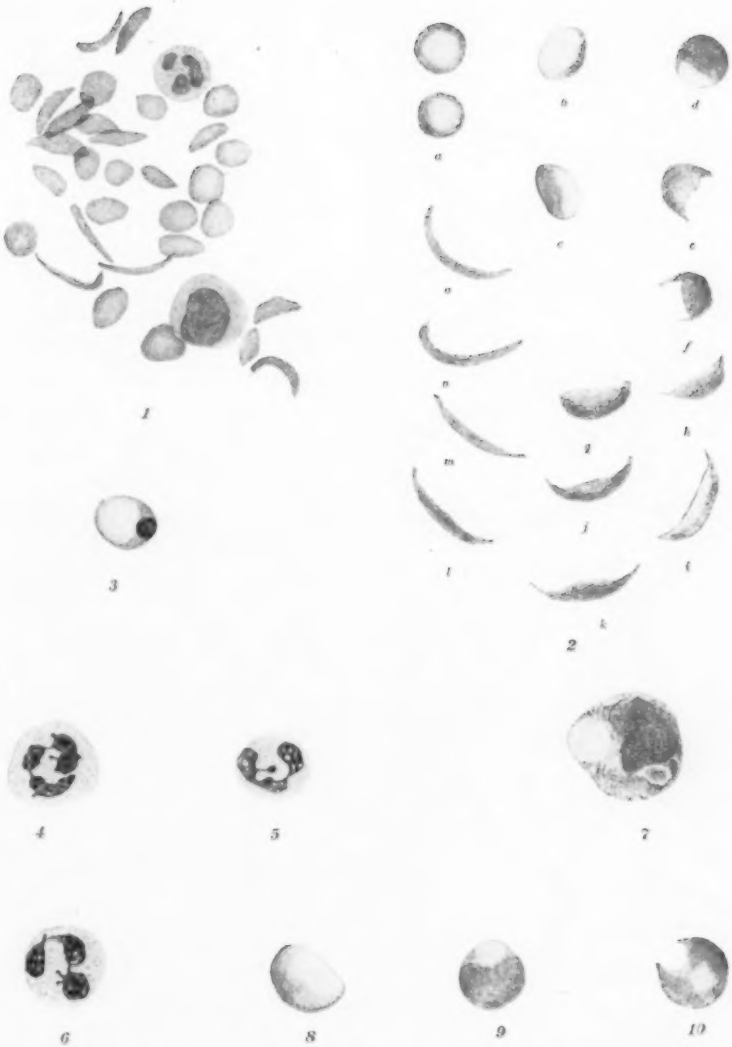

PLATE II

Figs. 11 and 12.—Five-day culture preparations of Erythrocytes from the patient's blood (11) and from normal blood (12). The bloods from the two sources had been placed in the same slide and were consequently kept under identically the same conditions. The crescentic and sickle-shaped forms increased in the case of the patient's blood, but no corresponding changes occurred in the normal blood. A characteristic feature in the former is the presence of tapering pointed tips at the extremities of the elongated and crescentic elements.

Figs. 13, 14, and 15.—Erythrocytes from twenty-four-hour cultures of patient's blood. Figure 13 shows face (*a*) and profile (*b*) views of the same corpuscle. A thickened rib-like rim is to be observed at one side of the disk. The remaining opposite side of the disk presents a thin transparent margin. The crescentic erythrocyte in Figure 14 presents a similar thickened and thin margin, together with a tapering pointed extension of the tips of the crescent. Figure 15 illustrates a more irregular form occurring in the cultures.

Fig. 16.—Face (*a*) and profile (*b*) views of an erythrocyte from a culture of the patient's blood in normal serum.

Fig. 17.—Illustrates the condition of the patient's blood in December, 1915, at which time the crescentic and sickle-shaped elements had temporarily almost entirely disappeared from the circulation.

Fig. 18.—Eight day culture from the patient's blood, December, 1915. Compare with Figure 17 and note the transformation into the elongated and crescentic erythrocytic elements.

Fig. 19.—Erythrocytic forms in a six-hour culture. Made at the same time that the preparations for Figure 17 were taken.

PLATE 2

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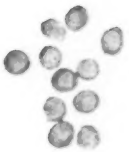

12

a b

13

14

15

a b

13

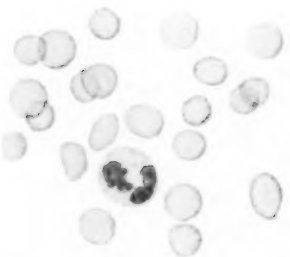

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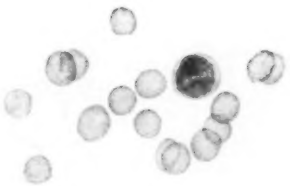
PLATE III

Fig. 20.—Drawing from a stained preparation of the patient's father's blood made in December, 1915.

Figs. 21, 22, and 23.—Twenty-four-hour cultures of father's blood, December, 1915. Shows the tendency on the part of some of the erythrocytes to assume elongated and crescentic forms.

Fig. 24.—From the same cultures as in the preceding figure showing the occurrence of certain irregular or crenated (?) forms.

PLATE 3



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REMARKS ON THE CHOLESTEROL CONTENT OF HUMAN BLOOD*

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Judging from the extensive literature which has accumulated on cholesterol during the past ten years, this lipoid has been the subject of more varied and extended investigations than any other substance of physiologic importance. Although it has received the attention of organic and physiologic chemists and clinical investigators alike, its exact constitution and much concerning its rôle in normal and abnormal metabolism remains to be solved. It is known, however, that cholesterol is a monatomic, simple, unsaturated, secondary alcohol. It further possesses the character of a complicated terpene, which gives it a unique position in the animal organism, since no other substance has been found to have so complicated a carbon nucleus except cholic acid, which alone is analogous.

The importance of cholesterol is indicated by its widespread occurrence in the animal body. Cholesterol is obviously, therefore, a constituent of our various animal foods, from which probably much of the cholesterol of the body is derived. According to Fraser and Gardner,[1] the phytosterols of the plant foods are transformed to cholesterol in the body, evidently furnishing a portion of our supply of this substance. Whether or not cholesterol is synthesized in the body, remains a disputed question. Lifschütz[2] believes that it may be formed from oleic acid, and also that it holds some genetic relationship to cholic acid,[3] since the same color reactions may be obtained after oxidation with benzoyl peroxid. In testing out the possibility of a transformation of cholesterol to cholic acid, Goodman[4] found that cholesterol, injected directly into the circulation, appeared to have but slight influence on the elimination of cholic acid. Rosenbloom and Gies[5] have also discussed the possible derivation of cholic acid and

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1. Fraser, M. T., and Gardner, J. A.: Proc. Roy. Soc., London (B), 1910, **82,** 559; Ellis, G. W., and Gardner, J. A.: ibid., 1912, **85,** 385.
2. Lifschütz, J.: Ztschr. f. physiol. Chem., 1908, **55,** 1.
3. Lifschütz, J.: Ztschr. f. physiol. Chem., 1914, **92,** 383.
4. Goodman, E. H.: Beitr. z. chem. Physiol. u. Path. (Hofmeister's), 1907, **9,** 91.
5. Rosenblom, J., and Gies, W. J.: Biochem. Bull., 1911-1912, **1,** 51.

bile salts (cholates) from cholesterol. They suggest that gallstones may arise when, among other causes, the transformation of cholesterol into bile salts is materially diminished, with a consequent marked increase in the concentration of cholesterol in the bile.

Satisfactory methods for the estimation of cholesterol have been, until recently, unavailable, and to Windaus[6] is due the credit of introducing the first procedure for its quantitative estimation, dependent on the fact that the digitalis glucosid, digitonin, forms an insoluble compound with cholesterol, which may be filtered off and weighed. With the more extended use of colorimetric methods, the Liebermann-Burchard and Salkowski color reactions have been utilized as the basis of methods of estimating cholesterol, the former by Grigaut[7] and the latter by Weston.[8] Since these reactions are very delicate, they at once afforded a means of estimating the cholesterol in small amounts of blood, thus furnishing a great impetus to this type of investigation. Of the two color reactions, the Liebermann-Burchard appears to have found somewhat greater favor, although both have been extensively employed. In the case of the digitonin method of estimating the total cholesterol, saponification of the cholesterol esters is necessary, since only the free cholesterol is precipitated by the digitonin. Cholesterol esters give the color reactions as well as does the free cholesterol. This fact does not appear, however, to have been recognized until very recently, since the directions for the colorimetric estimations have invariably called for a preliminary saponification. As pointed out by Bloor,[9] this saponification is unnecessary and the colorimetric estimation of the cholesterol thus becomes further simplified. More recently Bloor and Knudson,[10] by carrying out the colorimetric determination on extracts before and after the removal of the free cholesterol with digitonin, have been able to effect a simple estimation of both the free cholesterol and its esters. Despite the advances that have been made in improving the analytical technic of estimating cholesterol in the blood, there still seems to be some question as to the reliability of the absolute values reported. This point will be discussed in connection with the method which we have employed. It is believed, however, that the data on record are sufficiently accurate to warrant, in general, the conclusions that have already been reached.

Cholesterol occurs in the blood in both the free and combined state Free cholesterol is present in the corpuscles and to some extent in the

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7. Grigaut, A.: Compt. rend. Soc. de biol., 1910, **68,** 791, 827; 1911, **71,** 513.
8. Weston, P. G.: Jour. Med. Research, 1912, **26,** 47; Weston, P. G., and Kent, G. H.: ibid., 531.
9. Bloor, W. R.: Jour. Biol. Chem., 1916, **24,** 227.
10. Bloor, W. R., and Knudson, A.: Jour. Biol. Chem., 1916, **27,** 107.

plasma, and the cholesterol esters in the plasma alone. Bloor and Knudson[11] have found that in the whole blood the average percentage of cholesterol in combination as esters was about 33.5 per cent., and in the plasma 58 per cent. of the total cholesterol. Most of the data recorded in the literature, however, are for the total cholesterol of the blood, some of the results being on the plasma or serum, others on the whole blood. Normally, the concentration of cholesterol is nearly the same in the plasma and the whole blood, although, if anything, the plasma content is slightly higher and, pathologically, it seems to be subject to somewhat greater variations. When cholesterol or its esters are fed in solution in oil or in natural solution, as in egg yolk, the cholesterol is absorbed from the intestine through the chyle[12] and brings about an increase in the cholesterol of the blood.[1, 13]

The normal value for the cholesterol of human blood has been regarded, until very recently, to be about 0.15 per cent. The average value found by Bloor[14] for normal men was 0.21 per cent. and for normal women, 0.23 per cent. Although 0.15 per cent. is probably too low a figure, it would seem that the figures of Bloor were too high, and that possibly 0.16 or 0.17 per cent. may more nearly represent the true value for the cholesterol of human blood. Pathologically, a great many conditions have been recorded in which a hypercholesterolemia was found, while in a few conditions hypocholesterolemia has been noted. In general, it may be stated that hypercholesterolemia is found in arteriosclerosis, nephritis, diabetes, especially with acidosis, obstructive jaundice, in many cases of cholelithiasis, in the early stages of malignant tumors and in pregnancy. The chief condition in which low values for cholesterol are found is anemia. Further discussion of these pathologic variations will be taken up in connection with our own results.

As already pointed out, there appears to be some question as to the reliability of the absolute values reported in the literature for the cholesterol of the blood. It would appear that many of the results are somewhat low, owing to incomplete extraction of the cholesterol or possibly, as suggested by Bloor,[9] to destructive action on the cholesterol of the alkali employed in the preliminary saponification. Bloor has recently suggested a method of extraction for the cholesterol which is very simple and would appear to be very complete, but the results obtained with the method are higher than those obtained with the older methods, and rather irregular, owing, apparently, to the presence in

11. Bloor, W. R., and Knudson, A.: Jour. Biol. Chem., 1916, **29,** 7.
12. Mueller, J. H.: Jour. Biol. Chem., 1915, **22,** 1.
13. Lehman, E. P.: Jour. Biol. Chem., 1913-1914, **16,** 495.
14. Bloor, W. R.: Jour. Biol. Chem., 1916, **25,** 577.

the extracts used of substances interfering with the Liebermann-Burchard color reaction. According to investigations of Luden,[15] these probably result from a combination of the bile pigments and bile acids.

Our first analyses carried out in 1913 (data on pellagra, Table 8) were made according to the technic given by Autenrieth and Funk,[16] but the subsequent determinations (1914-1915) were made according to the simple technic outlined later. The results with this method were uniform and compared favorably with figures given in the literature, but in carefully checking up the results, it was found that the simple extraction as carried out, was incomplete. The results, however, are comparative and it is believed sufficiently accurate to allow a discussion of the general subject.

METHOD OF ESTIMATING THE CHOLESTEROL

The technic which was employed for the estimation of the cholesterol in most of the present series of experiments, was carried out as follows:[17] 2 c.c. of the oxalated blood were pipetted into a porcelain crucible of 50 c.c. capacity, 10 c.c. of 10 per cent. sodium hydroxid added, the mixture thoroughly stirred with a small glass rod and then placed over a boiling water bath for two hours to bring about the saponification of the cholesterol esters and solution of the protein material. At the end of this time about 15 gm. of plaster of Paris, were slowly added with constant stirring to prevent caking. When this was allowed to stand at room temperature over night, or placed in the drying oven at 90 F. for one hour, the mixture became a perfectly dry and very fine powder. The powder was transferred to a 250 c.c. bottle with stopper, 50 c.c. of chloroform added and the mixture thoroughly shaken for several minutes at intervals during a period of about two hours, after which the mixture was filtered into a perfectly dry cylinder or test tube through a dry filter paper. Five c.c. of this filtrate were employed for the colorimetric estimation as described later.

With the method just outlined, the extraction does not appear to be complete, the results being uniformly somewhat low (apparently about 15 per cent.). To insure complete removal of the cholesterol, a simple, continuous extractor is now employed.[18] Since, as Bloor has pointed out, the cholesterol esters give the color reaction as well as the free cholesterol, saponification is unnecessary and is omitted. One c.c. of blood is pipetted into a crucible containing about 4 to 5 gm. of plaster of Paris, stirred and dried. It is now emptied into a small extraction shell (4 cm. long) and then inserted in a short test tube (2.5 by 6 cm.), in the bottom of which are a number of small holes. This is now attached to a large cork on a small reflux condenser and the tube and cork inserted in the neck of a 150 c.c. extraction flask containing about 20 to 25 c.c. of chloroform. Extraction is continued for about twenty minutes on an electric hot plate, the chloroform made up to some suitable volume, such as 20 c.c., filtered, if necessary, and colorimetric estimation carried out as described below.

Five c.c. of the chloroform extract are pipetted into a dry test tube and 2 c.c. of acetic anhydrid and 0.1 c.c. of concentrated sulphuric acid (best with a 0.1 c.c. pipette) added. After thorough mixing, the solution is placed in the dark for ten minutes to allow the color to develop. It is then compared against

15. Luden, G.: Jour. Biol. Chem., 1917, **29,** 463.
16. Autenrieth, W., and Funk, A.: München. med. Wchnschr., 1913, **60,** 1243.
17. Myers, V. C., and Gorham, F. D.: The Post-Graduate, 1914, **29,** 938.
18. The details of this method will be described in a paper to be published.

a standardized aqueous solution of naphthol green B in a Hellige colorimeter. This excellently matches the cholesterol color and appears to be permanent, whereas cholesterol solutions in chloroform quite rapidly deteriorate. The solution of the dye employed was 0.0118 per cent. Employing a standard of this colorimetric strength (practically identical with that obtained from a 0.08 per cent. chloroform solution of cholesterol), the following formula, in which R represents the colorimetric reading, may be used to compute the cholesterol in the 5 c.c. of solution employed: $103 - R \times 0.00847 =$ mg. of cholesterol in 5 c.c. of chloroform.

DISCUSSION OF RESULTS

As will be found in Table 1, the cholesterol content of the whole blood of fourteen normal subjects, taken at random and not on special diet, varied from 0.13 to 0.19 per cent., with an average of 0.15 per

TABLE 1.—NORMAL SUBJECTS

Case	Age	Sex	Cholesterol of Blood, per Cent.
72 E. H.	51	♀	0.13
3 A. H.	65	♂	0.14
27 E. R.	41	♀	0.14
77 S. E.	26	♂	0.14
106 E. S.	26	♂	0.14
125 K. P.	15	♀	0.14
140 M. K.	26	♂	0.14
139 B. W.	26	♀	0.14
42 A. T.	31	♂	0.15
59 M. E.	33	♀	0.16
144 C. L.	28	♀	0.16
182 F. S.	20	♀	0.16
170 D. N.	55	♂	0.17
15 M. W.	28	♂	0.19

cent., figures which compare favorably with data reported in the literature (excepting the results of Bloor[14] and Denis[19]). As already pointed out in connection with a discussion of the method we have employed, these figures are probably slightly low, and 0.16 or 0.17 per cent. probably more nearly represents the true average for these subjects. For comparison with our own data on pathologic cases, however, 0.15 per cent. will be considered as the average normal.

In Table 2 are collected data on ten cases showing arteriosclerosis. A tendency toward hypercholesterolemia is evident when one compares

19. Denis, W.: Jour. Biol. Chem., 1917, **29**, 93. This paper gives the important literature references.

the figures with those of the normal cases given in Table 1. The figures are comparable with those given by Schmidt.[20] Just what relation there is, if any, between hypercholesterolemia and arteriosclerosis is not apparent. It is worthy of note, however, that histologic changes have been noted in the aorta after the experimental administration of cholesterol.[21]

In Table 3 data are recorded for the blood cholesterol on fifteen miscellaneous cases of nephritis. Most of the results obtained in these cases are quite above our normal findings. As will be noted in the

TABLE 2.—ARTERIOSCLEROSIS

Case	Age	Sex	Blood Pressure		Phthalein Output 2 Hrs., per Cent.	Cholesterol in Blood, per Cent.
			Systolic	Diastolic		
79 F. S.	66	♂	106	74	22	0.26 0.23 0.18
105 M. H.	71	♀	180	136	..	0.22
71 L. W	62	♀	148	62	67	0.21 0.18
142 E. K.	66	♀	156	106	..	0.19
83 L. B.	64	♀	200	164	56	0.18
174 A. P	50	♂	146	88	58	0.18
192 J. M.	55	♂	178	112	30	0.18
197 N. A.	52	♂	172	122	52	0.17
88 E. J.	58	♂	146	128	..	0.16
108 G. S	57	♂	158	112	..	0.16

table, there is no apparent relation in this series between the cholesterol and the blood pressure or nitrogen retention. Excepting the observations of Denis,[19] who found the cholesterol increased in only one case of nephritis out of a very large series, the observations recorded harmonize very well with data reported in the literature.[20, 22]

The few observations we have made on diabetes are recorded in Table 4. Hypercholesterolemia was present in four of the eight cases, and it is of interest that it was these four cases which showed evidence

20. Schmidt, H. B.: The Clinical Study of Hypercholesterinemia. THE ARCHIVES INT. MED., 1914, **13,** 121.

21. Anitschkow, N.: Deutsch. med. Wchnschr., 1914, **40,** 1215; Means, J. W., and Klotz, O.: Jour. Med. Research, 1916, **34,** 41.

22. Chauffard, A., Laroche, G., and Grigaut, A.: Compt. rend. Soc. de biol., 1911, **70,** 108; Widal, F., Weill, A., and Laudat, M.: Semaine méd., 1912, **32,** 529; Bacmeister and Henes: Deutsch. med. Wchnschr., 1913, **39,** 544; Klinkert, D.: Berl. klin. Wchnschr., 1913, **50,** 820; Cantieri, C.: Wien. klin. Wchnschr., 1913, **26,** 1692; Henes, E.: New York State Jour. Med., 1915, **15,** 310.

of acidosis. Since, as pointed out by Bloor,[23] the cholesterol increases along with the other blood lipoids in diabetic lipemia, the cholesterol may be taken here as an index of the lipoid content of the blood.

Considerable discussion has arisen with regard to the cholesterol content of the blood in cholelithiasis. Henes[24] has maintained that a

TABLE 3.—NEPHRITIS

Case	Age	Sex	Type of Nephritis	Blood Pressure		Phthalein Output 2 Hrs., per Cent.	Blood Urea N., Mg. to 100 C.c.	Blood Creatinin, Mg. to 100 C.c.	Date 1914-1915	Cholesterol of Blood, per Cent.
				Systolic	Diastolic					
82 W. F.	25	♂	Mercuric bichlorid	155	70	..	219	28.1	Nov. 13 Nov. 16 Nov. 23	0.34 0.22 0.20
81 E. E	30	♀	Interstitial; edema	214	154	10	102	5.3	Dec. 16 Jan. 11	0.28 0.26
12 E. B.	24	♂	Interstitial	241	116	14	...	....	Oct. 5	0.28 0.25
124 F. S.	67	♂	Interstitial	114	77	22	10	1.5	Nov. 14 Dec. 15	0.26 0.18
113 I. D.	17	♀	Interstitial	192	130	0	209	20.0	Dec. 21 Dec. 30 Jan. 3	0.18 0.22 0.21
111 G. P.	22	♂	Parenchymatous	...	...	53	21	....	Dec. 10	0.23
100 T. D.	34	♂	Interstitial	195	120	3	66	8.3	Jan. 15 Jan. 26 Feb. 12	0.17 0.19 0.18
138 L. R.	45	♂	Diffuse	196	125	47	24	4.2	Dec. 26 Jan. 11	0.15 0.19
187 M. F.	52	♀	Diffuse	162	112	45	...	....	Dec. 21	0.19
204 J. B.	34	♂	Interstitial	185	95	5	49	7.2	Apr. 3 (17)	0.19
64 L. B.	64	♀	Interstitial	260	164	56	16	3.1	Dec. 28	0.18
150 L. P.	62	♂	Diffuse	185	...	0	80	4.8	Jan. 6	0.18
184 L. S.	22	♀	Parenchymatous	148	128	22	...	3.1	Jan. 29	0.18
197 J. W.	34	♂	Interstitial	188	126	2	63	6.5	Feb. 24 Mar. 1	0.14 0.16
205 F. R.	32	♂	Interstitial	205	120	0	102	11.5	Apr. 2 (17)	0.15

hypercholesterolemia is almost invariably found in cases of cholelithiasis without fever. He has suggested that the hypercholesterolemia is the fundamental and primary etiologic factor in the formation of gallstones. In a more recent discussion of the subject, Rothschild and

23. Bloor, W. R.: Jour. Biol. Chem., 1916, **26,** 417.

24. Henes, E.: Jour. Am. Med. Assn., 1914, **63,** 146; Surg., Gynec. and Obst., 1916, **23,** 91.

TABLE 4.—Diabetes

Case	Age	Sex	Cholesterol of Blood, per Cent.	Urine		Blood Sugar, per Cent.	CO_2 Combining Power of Blood (Van Slyke)
				Acetone	Diacetic Acid		
180 R.	52	♀	0.22	+	+		
			0.18	+	−		
			0.18	+	−		
			0.19	+	−		
192 M. McC.	52	♀	0.19	+	+		
198 B. L.	..	♂	0.21	+	+		
191 D. W.	55	♂	0.16	−	−		
198 M. W.	..	♂	0.15	−	−		
207 H. R.	..	♂	0.35	..	..	0.30	34
206 M. B.	25	♀	0.14	..	..	0.18	54
206 V. A.	45	♂	0.11	..	..	0.25	50

TABLE 5.—Cholelithiasis

Case	Age	Sex	Jaundice	Time of Specimen	Cholesterol in Blood, per Cent.	Remarks
22 H. C.	44	♀	None	Anteoperation	0.13	Cholesterol stones found at operation
				Anteoperation	0.13	
				Postoperative 2 and 3 weeks	0.16	
				Postoperative 2 and 3 weeks	0.17	
26 G. K.	32	♂	None	Anteoperation	0.13	Cholesterol stones found at operation
102 V. O'Z.	32	♀	None	Anteoperation	0.14	Cholesterol stones found at operation
				Postoperation	0.16	
200 M. L.	32	♀	Slight	.....	0.17	Cholesterol stones found at operation
173 W. L.	15	♀	None	Anteoperation	0.18	Many cholesterol stones
				Postoperation	0.21	
2 A. R.	68	♀	Slight	.....	0.21	No operation
				.....	0.18	
4 E. P.	43	♀	Present	.....	0.22	No operation
68 M. J.	40	♀	None	.....	0.16	No operation
69 M. L.	44	♀	None	.....	0.18	No operation
98 R. S.	42	♂	Marked	.....	0.22	No operation

Rosenthal,[25] while admitting that many cases of gallstones show a hypercholesterolemia, point out that the exceptions are manifold, and that in their own series of thirty-seven cases, about a third did not show an increase in the cholesterol of the blood at the time the exam-

25. Rothschild, M. A., and Rosenthal, N.: Am. Jour. Med. Sc., 1916, **152**, 394.

ination was made. These authors emphasize the fact, however, that in a certain group of cases the hypercholesterolemia is very persistent and operation affords only temporary relief. They believe that properly selected diets (low in cholesterol) have been very beneficial in these cases.

It is not possible to draw conclusions from our own limited series of ten cases (Table 5). It will be noted, however, that only one of the five cases confirmed by operation showed a hypercholesterolemia, while in the remaining five cases those patients showing an increased blood cholesterol were jaundiced. The apparent influence of jaundice is shown in Table 6.

TABLE 6.—JAUNDICE

Case	Age	Sex	Type of Jaundice	Cholesterol of Blood per Cent.
87 F. T.	21	♂	Catarrhal	0.21
97 R. W.	23	♂	Catarrhal	0.19
110 R. K.	51	♂	Obstructive	0.29
131 J. N.	53	♂	Obstructive	0.17 0.18
99 A. H.	42	♂	Obstructive	0.16
107 C. R.	22	♂	Syphilitic	0.19

TABLE 7.—MALIGNANCY

Case	Age	Sex	Location of Growth		Hemoglobin (Sahli) per Cent.	Cholesterol in Blood, per Cent.
152 H. H.	47	♂	Stomach	Early	80	0.20
29 G. P.	43	♀	Stomach	Early	78	0.18
109 H. M.	53	♂	Esophagus	Early	90	0.18
14 I. L.	45	♂	Vertebrae	Early	90	0.18
5 R. M.	51	♀	Stomach	Early	85	0.17
57 H. F.	56	♂	Stomach	Early	86	0.15
46 N. K.	34	♀	Colon	Early	..	0.14
148 C.	50	♂	Pancreas	Late	..	0.16
56 E. K.	62	♂	Stomach	Late	..	0.13
135 H. H.	67	♂	Stomach	Late	72	0.13
102 A. O.	62	♀	Pancreas and stomach	Late	59	0.13
31 G.	44	♂	Stomach	Late	70	0.12
37 H. A.	56	♂	Stomach	Late	66	0.12
40 F. M.	37	♀	Esophagus	Late	65	0.12
67 M. L.	45	♂	Stomach	Late	80	0.12

From our own data on malignancy it would appear that among the early cases the blood cholesterol was normal or slightly above normal, while in the late cases the figures were somewhat below normal. This, in general, is the conclusion that has been reached by other workers.[26]

TABLE 8.—PELLAGRA

Case	Age	Sex	Severity of Condition	Cholesterol of Blood Serum, per Cent.
1 J. H.	45	♂	Mild	0.27
2 D. G.	28	♀	Moderately severe	0.24
3 J. O.	42	♀	Mild	0.21
4 J. S.	29	♀	Moderately severe	0.20
5 E. O'N.	32	♀	Moderately severe	0.18
6 E. B.	25	♀	Mild	0.18
7 S. E.	28	♀	Moderately severe	0.17
8 M. T.	19	♀	Moderately severe	0.11

TABLE 9.—SYPHILIS

Case	Age	Sex	Stage of Syphilis	Wassermann	Cholesterol of Blood, per Cent.	Remarks
24 N. G.	42	♀	I	Positive	0.17	
74 A. G.	20	♂	I	Positive	0.14	
142 C. D.	26	♀	I	Positive	0.13	
23 L. D.	23	♀	II	Positive	0.14	
22 C. C.	29	♀	II	Positive	0.12	
107 C. R.	22	♂	III	Positive	0.19	Congenital
17 L. C.	40	♂	III	Positive	0.17	
18 L. K.	25	♂	III	Positive	0.15	Gonorrheal arthritis
62 H. D.	25	♀	III	Positive	0.15	
91 M. C.	36	♀	III	Positive	0.15	
26 Z. K.	34	♀	III	?	0.15	
133 W. L.	48	♂	III	Positive	0.14	Aneurism
93 P. L.	27	♂	III	Positive	0.14	
147 S. S.	56	♂	III	Positive	0.13	
136 E. O.	28	♂	III	Positive	0.12	General paresis

Our cases of pellagra, the analyses of which were made in 1913, according to the technic of Autenrieth and Funk using a Duboscq colorimeter, show, with one exception, a tendency toward a hypercholestero-

26. Luden, G.: Jour. Lab. and Clin. Med., 1916, **1**, 662.

lemia. It is of interest in this connection, according to the observations of Fischl,[27] that the cholesterol content of the blood is high in the ordinary dermatoses not accompanied by fever.

The data which we have collected in Tables 9, 10 and 11 on syphilis, gastro-intestinal conditions and miscellaneous conditions, require com-

TABLE 10.—GASTRO-INTESTINAL CONDITIONS

Case		Age	Sex	Diagnosis	Cholesterol in Blood, per Cent.
5	M.	51	♀	Gastric ulcer	0.17
127	S. S.	44	♀	Gastric ulcer	0.13 0.17
86	A.	48	♀	Gastric ulcer	0.14
91	C.	36	♀	Gastric ulcer	0.15
118	A. K.	41	♀	Gastric ulcer	0.14
154	P. K.	35	♂	Duodenal or gastric ulcer	0.16
55	D.	29	♂	Duodenal ulcer	0.17
134	H. K.	38	♂	Duodenal ulcer	0.17
80	G.	45	♂	Duodenal ulcer	0.16 0.13
101	B. D.	34	♂	Duodenal ulcer	0.14
180	A. K.	37	♂	Duodenal ulcer	0.14
104	I. C.	62	♀	Colitis	0.13
58	F. S.	..	♀	Colitis	0.16
28	M. B.	27	♀	Colitis	0.14
90	D.	39	♀	Colitis	0.13
123	E. B.	19	♀	Colitis	0.13
129	R. B.	32	♀	Colitis	0.13
8	F. S.	47	♀	Colitis	0.12
119	H. S.	17	♂	Typhoid fever (18th day)	0.17
				Typhoid fever (28th day)	0.18
6	K.	29	♂	Typhoid fever (28th day)	0.13
				Typhoid fever (42d day)	0.16
7	R. L.	28	♂	Typhoid fever, 25th day	0.15
9	S. S.	51	♀	Typhoid fever, 33d day	0.14
33	E. W.	16	♂	Typhoid fever, 23d day	0.13

paratively little comment, since, with a very few exceptions, they are essentially all within normal limits. It may be noted in Table 11, however, that a hypercholesterolemia was found in two cases, one a case

27. Fischl, F.: Wien. klin. Wchnschr., 1914, **27**, 982.

TABLE 11.—Miscellaneous Conditions

Case		Age	Sex	Diagnosis, Remarks	Cholesterol in Blood, per Cent.
96	H. D.	45	♂	Acute alcoholism	0.14
44	P.	58	♂	Chronic alcoholism	0.13 0.13
64	W. L.	32	♂	Chronic alcoholism	0.17
126	W.	34	♂	Asthma	0.15
47	H. H.	32	♂	Acromegaly	0.14 0.14 0.16
78	R. C.	52	♂	Lymphatic leukemia	0.17
188	E.	33	♂	Myelogenous leukemia; fever	0.13
144	E. M.	54	♀	Lobar pneumonia	0.14
13	J. B.	57	♂	Gout	0.14
89	M. P.	47	♀	Gout	0.17
57	L. M.	19	♂	Brain tumor	0.16
18	L. C.	25	♂	Arthritis; syphilis	0.13
80	R.	40	♂	Chronic arthritis	0.12
122	A. R.	14	♀	Chronic arthritis	0.14
112	M. L.	17	♀	Chronic arthritis	0.16
187	A. M.	43	♀	Chronic arthritis	0.18
16	J. W.	12	♂	Trachoma	0.15
75	C. C.	16	♂	Imbecility	0.11
136	E. O.	28	♂	General paresis	0.12
52	R. C.	23	♀	Pregnancy, 9 months	0.18
60	L. S.	34	♀	Pregnancy, 8 mo.; eclampsia	0.23
40	F. M.	37	♀	Pregnancy, 3 mo.; malignancy	0.12
179	D.	24	♀	Pregnancy, 6 months	0.13
1	J. J.	34	♂	Cirrhosis of liver, hypertrophic	0.14
21	K.	28	♂	Cirrhosis of liver, alcoholic	0.17
44	P.	58	♂	Cirrhosis of liver, atrophic	0.13 0.13
19	B. O.	53	♂	Miliary tuberculosis; temp. 105 F.	0.26 0.27*
34	D.	35	♂	Pulmonary tuberculosis	0.14
73	C. D.	40	♂	Tuberculosis of glands of neck	0.14
132	J. B.	42	♂	Pulmonary tuberculosis	0.15
117	H. C.	26	♀	Pulmonary tuberculosis	0.16
143	L. S.	42	♂	Pulmonary tuberculosis	0.16
168	F. L.	14	♂	Tuberculous peritonitis	0.18

* Serum.

of pregnancy with eclampsia, and the other a case of miliary tuberculosis with fever.

That the cholesterol of the blood is lowered in anemia has been recognized for some time. The problem has already received considerable attention at the hands of Italian investigators, notably Antonelli[28] and Cantieri.[29] Cantieri noted beneficial effects after the administration of therapeutic doses of cholesterol ester, although there was little influence on the cholesterol of the blood serum. In her recent paper, Denis[19] noted subnormal values in primary and secondary anemias. She was unable to find any definite relation between the number of corpuscles or hemoglobin percentage and the cholesterol values.

TABLE 12.—PERNICIOUS ANEMIA

Case	Age	Sex	Hemoglobin (Sahli) per Cent.	Red Blood Cells	Cholesterol, per Cent.
61 J. H.	54	♂	46	2,140,000	0.061 whole blood
			44	2,930,000	0.052 whole blood 0.047 plasma 0.15 washed cells
165 O. G.	48	♂	40	2,368,000	1/28/15 0.07 whole blood 0.065 plasma 0.12 washed cells
			20	1,120,000	2/10/15 0.075 whole blood 0.07 plasma 0.13 washed cells
			..	1,200,000	2/17/15 0.072 whole blood 0.065 plasma 0.13 washed cells
182 F. S.	50	♂	34	2,080,000	3/24/15* 0.056 plasma 0.14 washed cells
			25	660,000	4/3/17 0.06 whole blood

* Day of splenectomy.

Our observations on pernicious anemia are given in Table 12. The finding of very low values for the cholesterol of the plasma, with essentially normal figures for the cells, would appear to be of considerable interest in this condition in view of the antihemolytic influence of cholesterol. For this reason we attempted to increase the content in the blood by feeding cholesterol to patient F. S., but as yet our data are insufficient to draw conclusions. It might be noted, however, that although there was no apparent increase in the blood cholesterol, there seemed to be some clinical improvement, in harmony with the findings of Cantieri. An interesting problem naturally suggests

28. Antonelli, G.: Policlinico, Rome, 1914, **21,** 341.

29. Cantieri, C.: Rassegna di clin., terap. e sc. affini, August, 1914, abstr., Zentralbl. Biochem. u. Biophys., 1915, **18,** 184.

itself as to the absorbability of cholesterol and other lipoids in anemias of the pernicious type. This general problem is being further investigated by one of us (G).

SUMMARY

Cholesterol estimations were made in the blood of about 200 patients, suffering clinically from about twenty-five different diseases. Hypercholesterolemia was observed, though not invariably, in arteriosclerosis, nephritis, obstructive jaundice and diabetes. A hypocholesterolemia was found in the cachexia of malignancy and all anemias of the pernicious type. The low cholesterol values encountered in the blood plasma of patients with pernicious anemia are regarded as of considerable significance, especially in view of the strong antihemolytic action of cholesterol. The findings in cholelithiasis were quite inconstant. Since hypercholesterolemia may be found in many conditions and is not uniformly constant in cholelithiasis, it would seem that the blood cholesterol possessed only a limited diagnostic usefulness in this condition. The estimation may possess some diagnostic value in diabetes, since the cholesterol serves as an easily determined index of any lipemia.

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THE TEMPERATURE METHOD IN THE LOCALIZATION OF A CARDIAC PACEMAKER*

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INTRODUCTION

The present study was undertaken to determine possible influences on the cardiac rhythm of heating remnants of the original sinus venosus tissue in the right auricle and neighboring parts other than the sino-auricular node. We have attempted in this work to control accurately the temperature, time of application and definite delimitation of the area affected. The work, in part, is also a critical analysis of this method of localization of a primary cardiac pacemaker, in view of the fact that in many previous studies of this character such accurate controls were not observed.

HISTORICAL

The method of accurate control of the temperature for localizing automatic tissue in the heart has not, so far as we are aware, been emphasized in any previous work. This method has been employed extensively by a number of investigators for localization of the primary pacemaker (MacWilliam,[1] Engelmann,[2] Adam,[3] Ganter and Zahn[4]); and for determination of variations in the seat of impulse formation under the influence of temperature changes within or outside the normal seat of impulse initiation (Jaeger,[5] Hering and Koch,[6] Flack,[7] Brandenburg and Hoffman,[8] Ganter and Zahn,[9] Zahn,[10] Meek and Eyster,[11] Lewis[12]). Finally, it has been used to determine the relation of the extrinsic cardiac nerves to the system of nodal tissues of the heart (Clark,[13] Flack,[7] Schlomovitz, Eyster and Meek[14]) and hinted at by Stewart.[15]

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1. MacWilliam: Jour. Physiol., 1888, **9,** 175 and 389.
2. Engelmann: Arch. f. d. ges. Physiol., 1896, **65,** 109.
3. Adam: Arch. f. d. ges. Physiol., 1906, **111,** 607.
4. Ganter and Zahn: Arch. f. d. ges. Physiol., 1912, **145,** 335 and 392.
5. Jaeger: Deutsch. Arch. f. klin. Med., 1910, **100,** 1.
6. Hering and Koch: Arch. f. d. ges. Physiol., 1910, **136,** 466.
7. Flack: Jour. Physiol., 1910, **41,** 64.
8. Brandenburg and Hoffman: Med. Klinik., 1912, **8,** 16.
9. Ganter and Zahn: Arch. f. d. ges. Physiol., 1913, **154,** 492.
10. Zahn: Arch. f. d. ges. Physiol., 1913, **151,** 247.
11. Meek and Eyster: Am. Jour. Physiol., 1914, **34,** 368.
12. Lewis: Heart, 1914, **5,** 247.
13. Clark: Jour. Physiol., 1912, **44,** 169; Heart, 1913, **4,** 379.
14. Schlomovitz, Eyster and Meek: Am. Jour. Physiol., 1915, **37,** 177.
15. Stewart: Physiology, Ed. 7, 1914, p. 158.

In a previous communication[16] we suggested that changes in cardiac rate may result from the application of heat to certain areas other than the seat of impulse initiation if the temperature is sufficiently high to increase the automaticity of these regions, and thus lead to possible erroneous conclusions as to the seat of the pacemaker as determined by this method. It would seem, therefore, of essential importance in the localization of the pacemaker by this method that the temperature range employed should not exceed or fall below the temperature of the tissue to such an extent as to affect extensive variations in the automaticity of the region affected and possible removal of the seat of impulse formation. This fact stood out clearly in our study[16] on the origin of the cardiac impulse in the turtle. More recently Eyster and Meek[17] have noted the inferiority of the temperature method as hitherto employed to the electrical method.

The idea that the pacemaker can shift from one position to another was an essential influence in carrying on the work reported. Gaskell was the first to emphasize a localized origin of the heart beat, and that the seat of this localization could be removed to other regions under certain conditions. The work of Gaskell, Engelmann, Lohman and others has shown that this may occur in one or both of two ways, either by depression of the automaticity within the normal pacemaker, or, in certain cases, by increase of inherent but dormant automaticity in other regions. So far at least as the mammalian heart is concerned, most workers believe that under all approximately normal conditions the pacemaker, even when removed from its normal seat, always resides within some part of the system of nodal tissues (Ganter and Zahn, Zahn, Meek and Eyster[18]).

METHODS

Six animals were experimented on—four dogs (puppies), one cat, and one rabbit. Ether was administered, and the thorax was opened under artificial respiration. The phrenic nerves were cut and the pericardium sewed back. A ligature inserted in the adipose tissue of the a-v groove was used to pull the heart gently to the left, thereby exposing the region of the great veins and right auricle. The exposure was similar to that shown by Brandenburg and Hoffman.[8] A receiving tambour connected by air transmission to a recording tambour received the auricle movements, the rate, from the appendix of the right auricle. A normal record was taken, and then a thermode was applied to a particular spot for a definite time interval. The heart, if influenced, was permitted to return to normal, and the thermode was again placed at the same or at a different spot. As a rule, the return to normal occurred immediately on removal of the thermode, or continued for several beats, never more than ten or fifteen, which was exceptional. This procedure was kept up until the end of the experiment. The copper tip C (Fig. 1) which was made from a bullet is 5 mm. long, and 1 mm. wide. One end of the tip was filed down giving an area of 1 square millimeter, which could be applied to heart tissue by holding the thermode at an angle.

Two ranges of temperature above body temperatures were used, a low range

16. Schlomovitz and Chase: Am. Jour. Physiol., 1916, **41,** 112.
17. Eyster and Meek: The Archives Int. Med., 1916, **18,** 796.
18. Meek and Eyster: Heart, 1914, **5,** 227.

and a high range, relatively. The various spots warmed are shown in Figure 2. It is possible that we were not always successful in applying the thermode in the coronary sinus, thereby reducing our results at that point.

In most cases the thermode was applied for five seconds, in some instances ten seconds, and in those instances in which the area comprising the head of the S-A node revealed unusual responsiveness, the thermode was kept there only one to three seconds. A stop watch was used to check the time during which the thermode was applied.

A control of our method seems to have been satisfied by the following considerations: The point VI was chosen because it has no specialized tissue. A rabbit was used in one experiment because the specialized tissue in its heart is in much more appreciable amount close to the inferior vena cava along the taenia terminalis, while in the other

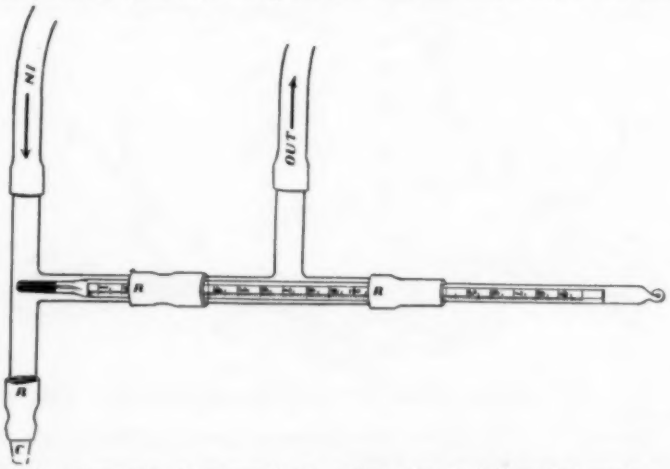

Fig. 1.—Thermode. C, copper tip; R, rubber tube; In, inflow; Out, outflow.

animals used the nodal tissue is most concentrated close to the angle formed by the right auricle and the termination of the superior vena cava. Therefore, in the rabbit the response at III should be marked, and this was found to be true. A probe, at room temperature, was applied at II (the spot most responsive) to see what effect a cooler object and especially irritation had. Spot II, known to be the position of the S-A node was found to be the spot at which rhythmicity could be influenced most easily.

The position and extent of the sino-auricular node, auriculoventricular node and associated structures have been so fully described by Keith and Flack,[19] Koch,[20] Lewis, Oppenheimer and Oppenheimer,[21]

19. Keith and Flack: Jour. Anat. and Physiol., 1907, **41,** 172.

20. Koch: Deutsch. med. Wchnschr., 1909, **35,** 429; Verhandl. d. Deutsch. Path. Gesellsch., 1909, **13**; Med. Klin., 1911, **7,** 447; 1912, **8,** 108; Arch. f. d. ges. Physiol., 1913, **151,** 297.

21. Lewis, Oppenheimer and Oppenheimer: Heart, 1910-1911, **2,** 147.

and others, that we have considered microscopic controls in our experiments as unessential.

A more accurate control of the two ranges of temperature could have been obtained by measurement of the temperature of the blood within the right auricle by means of a thermometer introduced through the azygos vein and superior vena cava. This we hope to do in subsequent experiments of this type, as well as in a series of atropinized animals.

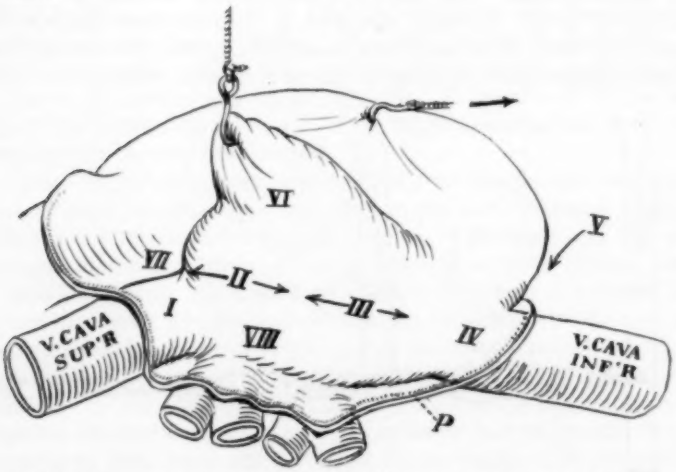

Fig. 2.—The numbers indicate where the thermode was applied. Diagramatic sketch.

I is made up of the anterior and right lateral portions of the sup. vena cava just before it empties into the auricle.

II is the area comprised in the right border of the upper half of the sulcus terminalis; the sinus nodal tissue proper.

III is the portion on the right border of the lower half of the sulcus terminalis adjacent to the inferior vena cava.

IV is the right lateral and anterior portion of the inferior vena cava just before it empties into the auricle.

V is part of the tissue covering the coronary sinus (the auricular portion of the A-V node).

VI lies in the main body of the right auricle.

VII is that termination of the superior vena cava which forms an angle with the auricle.

VIII is on the auricular tissue adjacent to the pericardial attachment below the termination of the superior vena cava.

In the rabbit the right superior caval vein was used.

RESULTS

Analyses of Experiments.—Table 1 is a summary of the procedures and results in a single experiment (F) on a dog.

TABLE 1.—Summary of Procedures and Results in Experiment F

No. of Tracing	Point at Which Thermode Was Applied	Temperature of Thermode, C.	Heart Rate		Percentage Increase in Rate
			Before Applying Thermode	After Warming	
1	Normal	..	180		
2	II	47	180—	240	33.4
3	III	47	190	185	—3.0
4	I	47	180	180	0.0
5	VII	47	195	200	3.0
6	II (3, 4)	47	180	200	11.0
7	II	47	180	220	22.0
8	VIII	47	185	175	—6.0
9	IV	47	170	170	0.0
10	V	47	170	180	6.0
11	VI	47	170	170	0.0
12	II	47	180	200	11.0
13	III	47	180	180	0.0
14	VII	47	175	180	3.0
15	IV	47	165	165	0.0
16	VI	47	160	160	0.0
17	V	47	160	160	0.0
18	VIII	47	160	160	0.0
19	II	46	160	200	25.0
20	IV	66	160	170	6.0
21	IV	71	160	175	9.0
22	IV	73	160	160	0.0
23	III	72	160	170	6.0
24	II (3, 4)	70	150	225	50.0
25	I	71	160	160	0.0
26	VII	71	150	150	0.0
27	II (3, 4)	70	145	225	55.0
28	II (3, 4)	66	155	220	42.0
29	II (3)	70	160	180	12.5
30	IV	65	140	150	7.0
31	V	66	150	150	0.0
32	III	66	150	150	0.0
33	VII	71	145	150	3.0
34	I	73	150	150	0.0
35	II	73	150	240	60.0
36	VI	71	150	140	—7.0
37	II (probe)	Room	140	140	0.0

TABLE 1.—Summary of Procedures and Results in Experiment F

No. of Tracing	Point at Which Thermode Was Applied	Temperature of Thermode, C.	Heart Rate		Percentage Increase in Rate
			Before Applying Thermode	After Warming	
38	III	70	140	140	0.0
39	VIII	72	150	150	0.0
40	IV	66	150	145	−3.0
41	IV	74	140	140	0.0
42	V	74	140	140	0.0
43	VI	72	140	140	0.0
44	VII	72	140	145	3.0
45	I	73	145	140	−3.0
46	VIII	73	140	140	0.0
47	VIII	74	140	150	7.0
48	IV	72	140	140	0.0
49	II	72	140	180	28.0
50	(5, 6)	74	140	184	31.0
51	VI	44	135	170	26.0
52	III	42	140	150	7.0
53	I	43	125	130	4.0
54	VII	43	130	130	0.0
55	IV	42	130	130	0.0
56	V	43	130	130	0.0
57	VI	43	125	130	4.0
58	III	43	130	130	0.0
59	II	42	140	170	21.0
60	(5, 6)	42	140	180	28.0
61	II (probe)	Room	Slight slowing	...	—
62	IV	72	125	130	4.0
63	IV	79	130	130	0.0
64	V	80	...	...	0.0
65	III	80	120	150	25.0
66	VIII	79	120	140	16.0
67	I	82	120	170	41.0
68	VII	82	120	140	16.0
69	V	82	120	120	0.0
70	II	82	110	160	45.0
71	VI	82	140	140	0.0
72	IV	80	140	140	0.0
73	II	79	135	180	33.0
74	Normal	..	130		

TABLE 2.—Analysis of Data After Being Tabulated as in Table 1

No. of Experiment	Point Warmed	Average Increase in per Cent. Over Normal		Highest Individual Increase in per Cent. Over Normal		Remarks
		Low Range	High Range	Low Range	High Range	
A	I	4	12	9	77	Cat, 3/19/16
	III	2	12	6	16	
	IV	0	9	0	16	
	V	3	—	7	—	
B	I	4	3	12.5	12.5	Dog
	III	0	8	0	17	
	IV	0	1	0	5	
	V	0	0	0	—	
	VII	0	—	0	11	
	VIII	0	0	0	0	
C	I	0	11	0	20	Rabbit
	III	18	45	57	50	
	IV	3	3	4	9	
	V	5	10	5	10	
	VII	14	28	14	28	
	VIII	5	6	10	12.5	
E	I	9	10	10	29	Dog
	III	2	11	10	27	
	IV	1	24	5	46	
	V	0	23	0	35	
	VII	14	10	48	14	
	VIII	1	6	5	29	
F	I	2	9	4	41	Dog
	III	3	8	10	25	
	IV	0	2	0	10	
	V	2	0	6	0	
	VII	2	5	3	16	
	VIII	3	5	6	16	
D	I	3	23	6	48	Dog *
	III	3	13	10	40	
	IV	7	3	8	14	
	V	0	4	0	8	
	VII	13	25	11	70	
	VIII	0	16	0	42	

* Pacemaker at S-A node up to 52 then heating had only slight effect at II, while a marked effect was obtained at IV and VII. After 52, the superior vena cava assumed power of contractility, beating, as it appeared to us, synchronously with the auricle. The heart rate was one-half of the normal rate, showing that the pacemaker was in the A-V bundle, but sinus tissue exclusive of the S-A node showed that it could assume impulse initiation.

Table 2 was compiled by analyzing the data for each experiment as in Table 1, and shows the increase of the rate per cent. over the normal produced by warming with the thermode, and using the low range and high range, respectively. This table is significant in that it shows increases at points outside of the S-A node at the same or lower temperatures used by other workers. Experiment E is especially striking.

Table 3 is a summary of part of Table 2 showing those points in each experiment where increases in rate were produced.

TABLE 3.—SUMMARY OF INCREASES SHOWN IN TABLE 2

Experiments	Points on Spots Warmed							
	I	II	III	IV	V	VI	VII	VIII
A Cat.....	+	*	0	0	—	00	—	—
B Dog.....	0	*	+	0	0	00	—	0
C Rabbit.....	+	*	*	0	0	00	+	0
D Dog.....	+	*	+	0	0	00	+	+
E Dog.....	+	*	+	+	+	00	0	+
F Dog.....	+	*	+	+	0	00	+	+
Totals (18)....	5	*	4	2	1	00	3	3

The table shows where increases in rate were produced by the use of the wider range of temperature. The stars indicate marked effectiveness at the sinus node. The double zeros show that absolutely no effect was produced on the auricle. The plus marks indicate that the heart rate was increased by warming at those points. The dashes indicate that that spot was not warmed in that particular experiment.

TABLE 4.—SUMMARY OF CERTAIN DATA OF THE EXPERIMENTS

Items	Experiments						Remarks
	A	B	C	D	E	F	
1. Heart rate per min.: Beginning of experiment.....	195	220	200	180	200	180	General decrease, never an abrupt drop
End of experiment...	160	160	220	140	120	130	
2. Warming at Spot VI	0	0	0	0	0	0	Auricle; no specialized tissue
3. Warming at Spot II given in per cent. increase	50	50	90(II) 57(III)	45	100	60	Always markedly positive
4. Temperature used, shown in 2 ranges: low (1, 3) high (2, 4) 1	52.5-64.5	53-55	50.5-52	50-55	37-55	46-47	
2	67-80	60.5-79	61-74	70-79	56-75	65-74	
3	50-63	52-54	52-53		42-47.5	42-44	
4					70-74	72-84	
5. Pacemaker throughout experiment at sinus node	Yes	Yes	Yes	Yes	Yes	Yes	Shown by its responsiveness

Table 4 summarizes the following data: (a) heart rate at beginning and end of experiments; (b) the fact that no change was produced by warming Spot VI which is auricular tissue; (c) the highest individual increase in per cent. produced at Spot II which is just over the head of the sino-auricular node; (d) the temperatures of the two ranges; and (e) the fact that the pacemaker remained at the sinus node as far as we could tell.

An examination of Table 3 will show that Spot II (on the sino-auricular node) was influenced by warming in such a way as to increase the auricular rate in all experiments. The next most effective region was Area I (termination of the superior vena cava); while the other regions were only influenced in half or less than half of the experiments. Spot VI (body of the right auricle) gave no reaction in any of the experiments.

At no time did we obtain an irregular heart by our method as far as we could tell. In a number of instances the heat increased the auricular rate so much that the ventricle did not follow with each impulse. In one case the sino-auricular node was eliminated by excessive heat, and the cardiac rate dropped to one-half of that existing previously.

The Efficiency of the Thermode.—The cardiac tissue is probably never heated up to the temperature point of the thermode in an interval of five seconds, and the same holds true for an interval of ten seconds. The particular area touched by the thermode absorbs heat, and it would be interesting to know how much of an increase in the temperature of a spot, as well as the amount of heat conducted to it, would be required to produce a certain increase in rate. To obtain an approximate idea of how much heat the thermode did convey we applied it to a thermometer with a long mercury bulb for five and ten second intervals. Briefly the results were as follows:

With a room temperature of 25 C., and a thermode temperature ranging from 46 to 73.5 C., the thermometer X showed an increase in temperature of 1 to 12 C., when its initial temperature ranged from 23.5 to 30 C. The greatest increases occurred with the thermode at the higher temperatures. Example: A thermode with a temperature of 43.5 C. raised the reading of thermometer X from 25.6 to 26.8 C. when applied for five seconds. This is an increase of 1.2 C. There is no doubt that this is a different proposition than when warming tissue covered with a film of moisture with an ever-changing blood supply, continuous cellular variations, and shielded by a thin layer of visceral pericardium. It is well known that the blood supply of the sinus tissue is very abundant. The probability is that with the low range temperature the sinus tissue was seldom raised above 1 to 2 degrees centigrade.

Certainly not enough heat was absorbed to be destructive. This was sufficiently indicated by the responsiveness of the S-A node, as well as the immediate or rapid return to normal rate.

DISCUSSION

Analysis of the Method.—One of the methods employed to determine the site of origin of the cardiac impulse in the warm-blooded heart was to warm circumscribed areas of the cardiac tissue. The temperatures employed ranged from 40 to 60 C. In a number of instances the temperatures are not stated. The time of application has also varied and in most cases is not stated. In Adam's tracings this time is shown to be from 12 to 50 seconds. As a result of this method the following data have been obtained:

MacWilliam,[1] on applying slight heat locally to the terminal part of the vena cava superior, obtained a marked acceleration in the rhythm of the whole heart, while a similar slight local cooling of the ventricular apex or any part of the ventricular substance gave no change in the cardiac rate. Adam,[3] working with this method before the sinus node was discovered, showed that the region most easily influenced is between the vena cavae, and that no results were obtained by warming or cooling the veins. Flack[7] reported that the normal dominating rhythm can be affected only at the S-A node. Ganter and Zahn[4] (p. 392) in a preliminary report state that every portion of the S-A node shares in the initiation of a normal heart beat. Koch discussed their report and said that the following seemed to him to be especially interesting, namely, that only the specialized tissue, the S-A node, manifests an influence on heart activity, while, on the other hand, influencing nearby tissue thermically, for example, the sinus remnant in the terminations of the large veins or auricle very close to the S-A node produced no typical effect on cardiac activity. Ganter and Zahn later published their experimental findings. If their sketches are compared with ours it will be seen that their points 1 to 5 correspond to our points II, III and VII (Fig. 2). They obtained an increased rate, especially at 1, 2 and 3 (equivalent to our VII and II). We obtained an increased rate at these points and at III and VII, especially when a higher temperature was used. They state again and again that at all other points warming and cooling had no influence. By systematic search they found the circumscribed spot known as the sinus node at which temperature stimuli produced a change in rate. Brandenburg and Hoffman[5] announced practically identical results at about the same time.

That such results are not due to conduction of temperature through the tissues has been shown by Engelmann, by Ganter and Zahn, by Schlomovitz and Chase,[10] and by us in the present paper. For example, in Experiment E, a temperature of 73 C. at points VI produced no

effect. So high a temperature certainly should secure response if this criticism is valid. Aschoff asserted that the indirect temperature effects in vessels supplying specialized tissue is of little importance, mainly because the same results are obtained with surviving hearts.

The above review reveals the citation of an unequivocal statement that only when heat is applied directly to the sino-auricular node can the rhythm be influenced (excluding the A-V system). A recital of a few facts will show, however, that the statement, with possible exception of that of MacWilliam, is not inclusive enough without a more careful qualification of the temperature in degrees, the tissue affected, or the time required to warm it. For example, this apparent contradiction has given rise to Erlanger's[22] criticism of the temperature method, in that it gives results that seem inconstant, for by it the rate of the heart may be affected over the terminal portion of the superior cava, over the node and near the inferior cava. The results are, however, consistent in this respect, namely, that they have been obtained only within the limits of the sinus reuniens. This statement, when analyzed, involves a criticism of the findings of all the workers following MacWilliam, and the fact also that in the rabbit a marked effect is obtained close to the inferior vena cava. MacWilliam specifies "slight heating" in one place without telling how the heat was produced and "hot galvanocautery" in another paper. To say "slight heating" is insufficient. The exact temperature and the exact period of its use should have been given. It is well known that when temperature reaches about 45 C. the quality of sensation is noted as *hot*. It is barely possible that MacWilliam in the stress of the experiment stopped to note the least perceptible difference in temperature from "warm" to "hot." It is, however, highly probable that he overshot the mark, 45 C., in his judgment of the sensation's quality. "Slight heating," then, as we interpret it, implies a temperature above 45 C., while "hot galvanocautery" may very well imply a temperature still higher, and therefore the temperatures used by MacWilliam may fall in our wider range, which make his findings agree with ours. The fact that results are obtained near the inferior cava in the rabbit is easily explained by the histologic picture as stated above.[20] With the qualifications, therefore, that the use of *proper* temperatures can produce impulse initiation in all of the sinus reuniens tissue, Erlanger's last sentence is true.

Somewhat the same kind of criticism could have been used in judging the results obtained by the temperature method on the cold-blooded heart, before we advanced data[16] that seemed to explain the apparently contrary results. When Engelmann[2] localized the origin of the heart beat in the frog by the temperature method — using a

22. Erlanger: The Archives Int. Med., 1913, **11**, 334.

galvano thermo cautery — he found that he could transfer the pacemaker from one point to another by warming the latter. This transfer, indicated by an increased rate, occurred after a latent period. We,[10] however, found that when a relatively low range of temperature was employed the rate could be influenced immediately and with no latent period at only one spot — the right sino-auricular junction — while with the use of a high range of temperature we could make the pacemaker appear after a latent period at various points on the sinus venosus and on the veins emptying into it. Such a shift of the pacemaker by proper thermic influence has been shown to occur in the sinus node itself[11] as well as from the sinus node to the a-v system. Also, in localizing the point of action of the vagi in the heart, cooling with various intensities yielded various results. These facts reveal the importance of proper interpretation. On the basis of work previously done on the cold-blooded hearts, we suggested that if any remnant of the sinus tissue in the normal warm-blooded heart be influenced so as to make it more automatic, it would either assume the pacemaking function or else it would in turn influence the primary pacemaker and thereby produce a change in heart activity. We found this to be the case as shown by our results. Other spots (I, IV, V, VIII) than the sinus node region were found, that, on being warmed, produced an increase in rate — a typical effect on cardiac activity.[20] This increase in automaticity, however, resulted when the high range of temperature was employed. With the low range only the sinus node was influenced. These results were produced by us repeatedly. Investigators in their search for a primary pacemaker warmed their thermodes up to 60 C. (the range being 40 to 60 C.). We found (Experiment E) that an increase in rate up to 22 per cent. could be produced at point IV with 56 C. We have obtained 2 to 10 per cent. increases at other points than the sinus node with temperatures close to 50 C., and for the purpose of finding a primary pacemaker even 50 C. is probably too high. A 10 to 20 per cent. increase in rate ought to be sufficient, and such increases are possible at temperatures even closer to body temperature. We have obtained such increases at 41 and 42 C. These results seem to indicate that in localizing the primary pacemaker with warm temperature the range should be a narrow one.

From results obtained by them in cooling and excising the sinus node, Brandenburg and Hoffman demand for all researches which are concerned with the significance of the sinus node as the point of origin of the normal cardiac impulses, that nondestructive methods be used, for only then will the results be clear and unequivocal. Previous to them Lewis[21] commented on the fact that a "dislocation" of the pacemaker occurred with slight provocation.

Corroborative Data of Sinus Tissue Rhythmicity by Other Methods.—The fact that sinus tissue, exclusive of the S-A node, can display typical cardiac activity (rhythmicity) is substantiated by the following data obtained by other methods. It is a well known fact that in attempting to find the region of the dying heart which retains its power of contraction longest, investigators discovered sinus tissue (mouths of vena cavae, and coronary sinus) not only contracting but contracting rhythmically. These results were noted by inspection, by registration, and by the electronegative method (for references see Footnote 23). In Experiment D, after the S-A node had been destroyed by heat, we noted the assumption of rhythmicity in the termination of the superior vena cava. Apparently, of all the sinus tissue the S-A node is unique in not having been observed to have the property of contractility. Gunn and Chavasse[24] found in the vessels examined by them that epinephrin causes quiescent rings of the superior vena cava only to beat rhythmically and powerfully, and that the rhythmically contractile tissue is comprised in a region for at least 6 to 8 mm. from the veno-auricular junction. Cow[25] had previously stated that the pulmonary artery shows rhythmical contractility after epinephrin is applied to it. Macht,[26] however, makes no statement of the production of rhythmical contractions by epinephrin on the pulmonary artery either in his review of the literature, or in his own experiments. Cow's records, rather, show that their interpretation is incomplete unless emphasis be placed again on the difference between tonic contractility and rhythmical contractility as Wharton Jones did in 1852.[27] MacWilliam[1] noted acceleration of the auricle in the heart in situ by stimulation, while Erlanger and Blackman[28] obtained the same results when using auricular strips obtained from the sinus region. Erlanger,[29] whose work was confirmed by Moorhouse,[30] excised strips containing sinus reuniens tissue from the mammalian auricle (cat, rabbit, dog) and inferred from his experiments that all the strips possess approximately the *same grade* of rhythmicity. This fact seems to be disproved;[17] nevertheless the fact remains that the sinus tissue is highly rhythmical. A coronary sinus rhythm has been demonstrated by Zahn[10] by the temperature method, and by Eyster and Meek[18] by the method of initial negativity. We believe that the potential significance of the sinus tissue exclusive of the S-A node has been brought

23. Eyster and Meek: Heart, 1914, **5,** 137.
24. Gunn and Chavasse: Proc. Roy. Soc. Med., 1912-1913, 86 B.
25. Cow: Jour. Physiol., 1911, **13,** 125.
26. Macht: Jour. Pharmacol. and Exper. Therap., 1914, **6,** 16.
27. Jones, Wharton: Philosoph. Trans., 1852, p. 131.
28. Erlanger and Blackman: Am. Jour. Physiol., 1907, **19,** 125.
29. Erlanger: Am. Jour. Physiol., 1910, **27,** 87.
30. Moorhouse: Am. Jour. Physiol., 1912, **30,** 358.

out in the diverse experiments in which there has been an attempt to produce the first Stannius ligature in the mammalian heart by destruction or elimination of the node and tissue closely related to it. Success in all cases seems to depend on effectual removal of all the sinus tissue or the parts important for conduction, and probably therein lies the cause for the increase in rate noted in experiments even after complete excision of the S-A node. Coronary sinus rhythm had been theoretically postulated by Edens, Rihl, and Lewis.

Origin of the Impulse in the Specialized Tissue.—When the temperature method is used, there seems to be some question as to whether or not the impulse arises at a narrow, definite point, or whether it is the resultant of the metabolic influences at play in all the sinus reuniens tissue, or all the sinus node. In a part or in all of this sinus musculature the heart rhythm is believed to be initiated.[10]

Ganter and Zahn[4] comment that the assumption of impulse initiation by a spot in the sinus node other than the head end *after warming* increases its automaticity is a reasonable view to take, but not quite so reasonable a view can be taken after cooling the same spot. They say that it is difficult to understand how a less automatic spot whose automaticity is further decreased by cooling can assume the pacemaking function. They explain the results by saying that normally every part of the sinus node contributes its definite share in the formation of an impulse, and therefore for each impulse a definite amount of energy is required and produced by the entire sinus node. Heat will develop this amount quicker, and cold contrariwise. They recognized the fact that Engelmann produced a shift of the pacemaker. The electronegative method, however, has shown that the pacemaker can shift even within the sino-auricular node itself.[11] If the electric potential which thus shifts is the sum of influences in the sinus tissue, as Ganter and Zahn claim, then it seems strange that *the heating* which is then merely heating the electric potential at that point should in turn change the activity of the entire tissue itself.

To What Extent Can Nerve Influences Be Excluded.—That there is an abundant supply of ganglia and nerve-fibers to the S-A node and the sinus tissue is well known (Meyer, Gaskell, Dogiel, Engelmann, Jolmann, Bethe, Carlson, Langley, Langendorff, Keith and Flack, Flack, Koch, Mönckenberg, Keith and Mackenzie, Mackenzie, Morison, Argand, Eyster and Meek, Meikeljohn, de Witt, Lewis, Oppenheimer and Oppenheimer, and others). This is true for the cold-blooded heart as well as the mammalian heart. With particular reference to the latter this much can be stated, that an appreciable portion of this ganglion and nerve-fiber supply is continuous with the vagi, sympathetics, and possibly depressor. Further, that these in turn — especially the chrono-

tropic fibers of the vagus and sympathetic — are in close relation to the S-A node (Flack, Rothberger and Winterberg, Ganter and Zahn, Marchand and Meyer, Cohn, Eyster and Meek, and Schlomovitz, Eyster and Meek). Another portion of the ganglion and nerve-fiber supply may be outlying stations ultimately connected with the nerves mentioned above, or with the S-A node, or both. If so, this would allow the possibility of local reflexes. Our conception of this distribution is naturally limited to the nerves named and the S-A node, since up to the present they only are recognized as entities, both anatomically and physiologically. In lieu of the above facts the location of the main paths of the inhibitory and accelerator cardiac nerves must be considered in relation to the influence especially of large temperature variations, as temperature alteration of such paths might influence the pacemaker indirectly. It is probably proved that atropin effectively rules out vagal activity on the heart. MacWilliam says that the response of the hearts to heating was the same in atropinized and unatropinized animals. Eyster and Meek report no differences in regard to the behavior of the pacemaker in atropinized and unatropinized animals. With the vagi intact it is possible to increase their efficiency by warming them and so cause a slowing of the heart, but the latter has not been confirmed by the experiments of MacWilliam, Adam, Ganter and Zahn, Zahn, and Brandenburg and Hoffman. In our experiments, out of a total of 412 readings there were 210 in which the high temperature range was used, and in eight of the latter, or 4 per cent., there was a decrease in rate of 3 to 11 per cent. (average 6 per cent.). The eight occurred in Experiments A, B, C, and F, while of the eight there were four in F alone. On the other hand, warming may increase the efficiency of the accelerator fibers and cause an increased rate either when there is simultaneous warming (a) of the vagi, or (b) of sinus tissue, or (c) of both, so that the automaticity of the sinus tissue is gradually increased until it becomes the pacemaker. Either (b) or (c) seem to be the explanation of our data where results were obtained only after a long latent period. The influence of the accelerators cannot be removed as easily as that of the vagi. We must wait for a drug as efficient as atropin without doing damage to the tissues, or else carry out a series of experiments with the accelerator mechanism effectively excluded (excision, etc.). The use of ammonia (Fredericq), cocain, nicotin, apocodein, etc., is discountenanced by Brandenburg and Hoffman, and by all those who consider the automatic tissues to constitute a delicate mechanism. In our present state of knowledge the accelerator mechanism in the cardiac tissue itself cannot be eliminated. This statement applies as well to the local reflex mechanisms that probably exist in the heart but have not yet been shown to be functional units. In addition to these

facts, it is difficult to administer a drug which we are certain has little effect on the S-A node or sinus tissue when used on nerve elements, or vice versa. In our experiments nerve influences were minimized by ether anesthesia, but not sufficient to make radical elimination. Therefore, we submit these facts as a basis for further research.

SUMMARY

Effect of Thermic Stimulation of Sinus Reuniens Tissue as Determined by the Methods Described.—

1. Thermic stimuli, with a temperature range above and close to that of the body, in the warm-blooded animal, will produce an increase in rate only when placed on the sino-auricular node. These are stimuli in a narrow temperature range, and at lower temperatures than heretofore employed.

2. Thermic stimuli considerably above body temperature will produce an increase in rate when applied on any of the sinus musculature in the mammalian heart. These are stimuli in a wider range. These results have also been obtained at the same temperatures used by other investigators in localizing the sinus node as the seat of impulse initiation and the only sinus tissue revealing typical cardiac activity.

3. It is important to note for how long a time thermic stimuli are applied.

4. Sinus tissue other than the S-A node when properly influenced by thermic stimuli will display the power of impulse initiation.

5. The response of a certain region may be the result of increase of its automaticity by the heat until it becomes the pacemaker, and does not necessarily mean that it was the seat of impulse initiation before the heat was applied.

We are glad to express our indebtedness to Professors Carlson, Eyster and Meek, of the Universities of Chicago and Wisconsin, respectively, for suggestions and assistance.

PYOPNEUMOTHORAX AND PNEUMOTHORAX

A REPORT OF TWO CASES WITH INTERESTING CLINICAL AND ROENTGENOLOGIC FINDINGS *

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Pneumothorax alone, or accompanied by serous fluid, or by pus, is infrequent enough in any single clinic to be of sufficient interest to study and report. In the present case of pyopneumothorax (Case 1) there is added interest on account of the obscured physical signs and symptoms, the unusual partial encapsulation of the pneumothorax, as shown by roentgenogram, and the transmitted cardiac pulsation through the fluid.

In the majority of cases the collapsed lung is easily discernible by Roentgen ray and can be made out by percussion near the mediastinal border, in contrast to the hyperresonant, tympanitic condition of the rest of the chest, and at the base of the pleural cavity the fluid can be easily marked out. In a typical case of pneumothorax, such as is reported here, and which preceded the present case of pyopneumothorax by a few weeks, diagnosis is not a difficult matter. When atypical complicated cases present themselves, diagnosis is increasingly difficult.

The normal pleura is not visible by roentgenography. When, however, pathologic changes occur, and there is thickening of the pleura, or when definite bands of adhesions result, then such changes are capable of being diagnosed by roentgenographic methods.

If there is serous fluid in the pleural cavity sufficient to give physical signs or symptoms, and if there is with it a pneumothorax condition, then the roentgenoscopic examination will determine it.

In partial pneumothorax conditions, pleural adhesions may, to a certain degree, limit the extent of both the air and fluid in the cavity. If the adhesions are along the median line, the displacement of the heart by the fluid and air is restricted; in cases in which the adhesions occur between diaphragm — especially in its central and dome portion — and pleura or mediastinum, a true comparison of the position of the diaphragm is impossible, and when adhesions extending transversely across the pleural cavity occur — especially in the upper one-third of the chest — the true extent of the pneumothorax and the position and the outline of the diseased lung cannot be determined. Likewise, is it impossible to determine the existence of tuberculosis

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in the upper lobe of the lung — if not collapsed — or in any part of the atelectatic lung.

The presence of large amounts of fluid adds to the difficulty of diagnosis, as a diagnosis of fluid in the pleural cavity, as such, is of little value unless the associated condition of the chest contents and their function can be given.

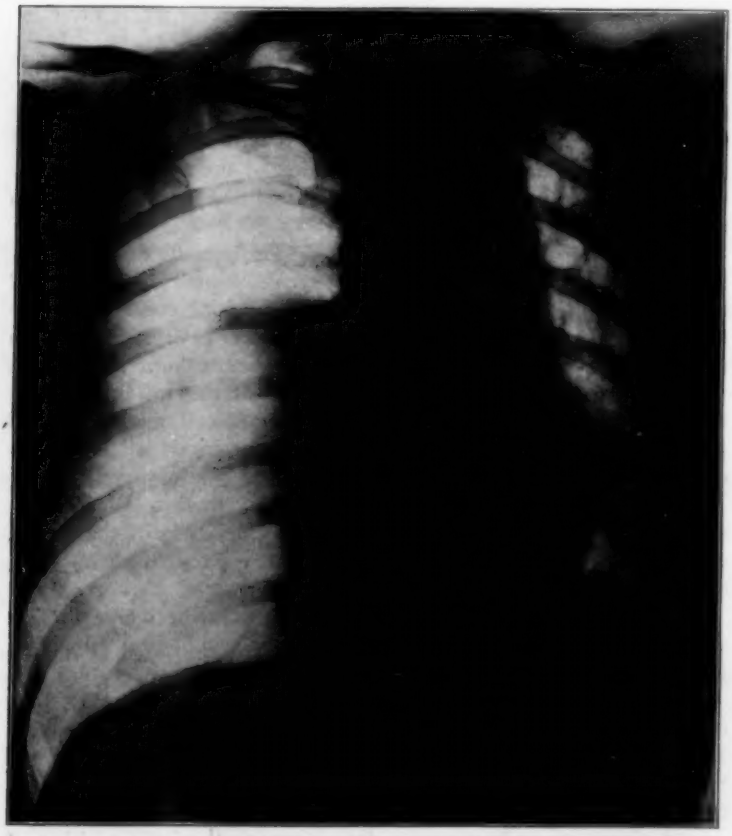

Fig. 1.—Case 1 (Hosp. No. 214). Pneumothorax of left chest; diaphragm at twelfth rib; collapsed lung visible between seventh and tenth ribs, near mediastinum; heart displaced to right.

In probably no other condition of the chest is the value of combined clinical and roentgenographic methods so well illustrated as in the pneumothorax, hydrothorax or pyopneumothorax cases. In Case 1, of pyopneumothorax, this is well brought out.

REPORT OF CASES

CASE 1.—(Hosp. No. 214.) *Pneumothorax.*

History.—March 8, 1917. Woman, aged 27, with a history of a slight attack of vomiting on March 3; no history of pain in the chest; patient has lost 15 pounds in the previous six weeks.

Physical Examination.—The patient is of fairly normal build and development. Physical examination shows a slight bulging of the left chest, with intercostal spaces flush with the ribs; the percussion note is higher pitched on the left and is tympanitic; respiration is faint, and amphoric breathing is heard over the entire left side; definite coin sound elicited. The heart is displaced to the right 10 cm. from the median line.

The roentgenograms show a marked contrast between the right and left lung. The right lung is dense—apparently compressed—as evidenced by the increased shadows at the hilus. Throughout the lung, and especially at the apex, definite mottling is seen. The left chest is transparent—a pneumothorax condition—and near the hilus is the more or less butterfly-wing outline of the atelectatic lung.

The heart and mediastinal vessels are displaced to the right to a considerable extent. The diaphragm on the left is lower than normal; the diaphragm on the right is higher than normal.

Diagnosis.—Pneumothorax, atelectasis. Probable pulmonary tuberculosis. Displaced heart.

March 9, patient aspirated and percussion of the heart shows it to be 7 cm. to the right of the median line; physical signs the same.

Roentgenograms show the heart slightly less displaced by approximately 1 cm. The collapsed lung is denser and the remaining left chest space is slightly less transparent. The costocartilaginous articulations show marked calcification.

On discharge (March 12) breath sounds over left lung still diminished and coin sound distinct; apex beat neither visible nor palpable.

CASE 2.—(Hosp. No. 291.) *Hydropneumothorax.*

History.—March 29, 1917. Man, aged 51, with history of shortness of breath for five weeks, which has been more marked in the previous three weeks; pain in left chest.

Physical Examination.—The patient is of normal build and fair development, but emaciated. Physical examination shows both apices to be sunken, clavicles prominent; dulness of right apex to the second rib; breathing is harsh and a few râles are heard at the right apex after coughing; tactile fremitus in right axilla; Grocco's sign on the right side; on the left there is dulness from the ninth dorsal spine downward, which is modified when the patient lies on his right side. There is visible and palapable pulsation of the chest in the left post axillary line from the middle of the scapula down to the base; heart displaced to the right.

Diagnosis.—The clinical diagnosis suggested possibly an aneurysm, pericardial effusion and pulmonary tuberculosis.

The patient was partially delirious and difficult to control; was unable to lie down, and suffered with frequent paroxysms of pain in the lower left chest, making the examination difficult both from a clinical and roentgenographic point of view.

The roentgenograms show the heart much displaced to the right. The displacement arises at the first rib and extends gradually and obliquely downward to the right base. The right heart outline is distinctly seen converging at right angles to the diaphragm. The lung on the right is not clear, although it is emphysematous and the diaphragm is very low. The left lung shows marked density and mottling at the apex and to the first space, where it is definitely demarcated by a dense semicircular line 1 cm. wide, which arises from the hilus region and extends upward and outward to the axilla. Below this curved

line there is a large, clear transparent area, more or less oval in outline, extending to the fifth rib. From the fifth rib downward great density occurs. The diaphragm is not discernible. Barium sulphate in emulsion was given the patient to determine the position of the fundus of the stomach; the roentgenograms show this organ to be situated low in the pelvis, and consequently bears no relation to the process above.

Fluoroscopic examination indicates the surface line of the fluid at the base to be more horizontal than appears on the roentgenograms, and with inspiration there is a slight movement of this line.

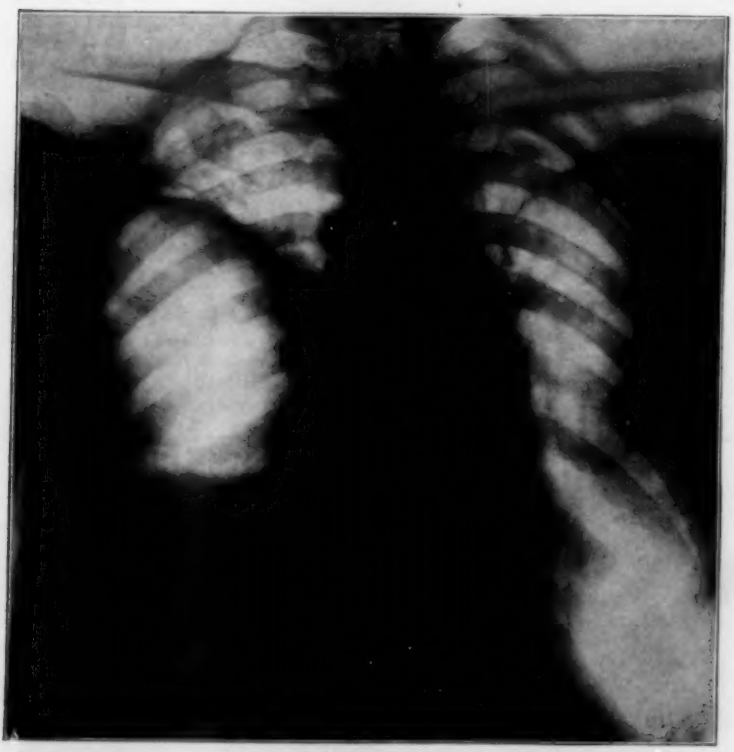

Fig. 2.—Case 2 (Hosp. No. 291). Hydropneumothorax. Patient erect; shows line of fluid on left at ninth space; band of adhesions seen transversely across upper part of chest from seventh rib near mediastinum to middle of scapula on the outer side; compensatory emphysema on the right; diaphragm at eleventh space; heart displaced to right.

Displacement of the heart to the right as shown in this case, without greater symptoms and physical signs, does not suggest aneurysm. The heart outline on the right, especially at its juncture with the diaphragm, suggests some fluid in the pericardium. The density at the left apex and the zone of transparency below this indicates a pneumothorax—atelectasis of the lower lobe—with fibrous

adhesions encapsulating the pneumothorax area. The greater density at the base is probably fluid.

The pulsation cannot be explained in any other way than that it is transmitted through the fluid to the outer chest wall from the heart. Were the pulsation present in the upper axilla only, it might be explained by the fibrous adhesions and compressed lung.

April 3. Clinical examination elicits a shifting dulness at the base when the patient shifts his vertical position to the semiprone or horizontal. Above this area a definite coin sound is now obtained; succussion is heard. The roentgenographic diagnosis is verified.

Fig. 3.—Case 2 (Hosp. No. 291). Hydropneumothorax. Patient prone, shows fluid throughout left chest to the curved band of adhesions. For comparison with Figure 2.

April 5. The patient is aspirated and approximately 11 ounces of foul-smelling pus removed.

April 6. Repeated roentgenographic examination shows the following changes: The density of the left base extends perhaps a little higher, and the density of the upper left lung and the whole of the right show a more detailed mottling than previously seen. With the patient in the prone position the roentgenogram shows that the density seen previously at the left base has extended upward and is now apparent throughout the whole of the left chest,

even extending beyond the curved zone previously described. This definitely proves the presence of free fluid in the left pleural cavity.

April 7. Resection of ribs. Operative findings: Pleural cavity contains about 1,000 c.c. of very foul, moderately thick pus. The upper lobe of the left lung, as far as could be felt, collapsed, but apparently normal. The lower lobe of the left lung is partially destroyed, the remaining portion being very much infiltrated. The heart is displaced beyond the vertebral column to the right; pericardium much thickened and contains a moderate amount of clear fluid; heart about normal, in size, and there is a dense adhesion between the apex and pericardial side. The patient died on this date.

It is of interest to note that an almost identical case of hydropneumothorax is reported by Aimé,[1] occurring in a French soldier infected with pulmonary tuberculosis. The pleural cavity was divided by a fibrous band extending from the diaphragm upward to the compressed lung, forming an outer and an inner air pocket; also dividing the fluid at the base of the lung into two portions. The diagram and roentgenogram are reproduced here.

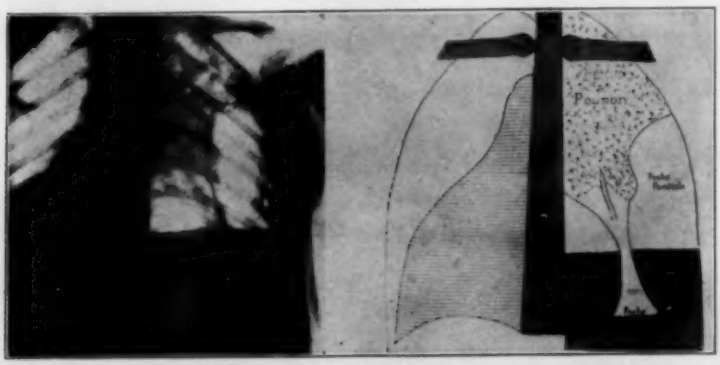

Fig. 4.—On the left, roentgenogram of Aimé's case of right hydropneumothorax with pockets. At the right is a tracing of the figure on the left.

In respect to the pulsation described in Case 2 (Hosp. No. 291), a very interesting article is reported by W. P. Herringham.[2] Among other cases he reports one of pulsating hemopneumothorax in a soldier, as follows:

Hit July 29, 1916, by a bullet on the outside of left shoulder. Hemoptysis followed.

July 30. Heart's apex impalpable; right border a little displaced to the right (by percussion and auscultation). Lungs: right, front, natural; left, front, surgical emphysema obscured everything.

1. Aimé, P.: Right Hydropneumothorax wtih Several Pockets in a Tuberculous Individual, Jour. de radiol. et d'electrol., 1916, **2**, 323; abstr., Am. Jour. Roentgenol., 1917, **4**, 199.

2. Herringham, W. P.: On the Early Stage of Wounds of the Chest, Quart. Jour. Med., 1916-1917, **10**, 79.

August 5. On the left side an impulse thought to be due to the cardiac apex was felt in the fifth space. The usual cardiac dulness seemed to be present. It was continuous with the impairment of the left side and back. The upper front was tympanitic. There was no breath sound; no bell sound. Pulsation was palapable up to the clavicle.

August 6. The left side was bulging still and there was a slight local prominence under the clavicle. Pulsation as on August 5, but the heart was obviously beating on the right side as far out as the nipple line. The impulse felt in the left fifth space both August 5 and 6 could not therefore be cardiac. It was the same as the impulse felt in the upper resonant area. An occasional tinkling sound was heard.

August 8. Same signs; well-marked succussion splash both heard and felt; general condition excellent; no distress; temperature normal. Evacuated to base.

The author then concludes by stating that "Pulsating empyema is known, but I have never heard of pulsation in a pleura containing air and blood. When the pulsation was first noticed my colleagues in the clearing station and I held long consultations over the case. We could think of no known condition likely to produce it except aneurysm. But the impulse was not like that of an aneurysm; there was no bruit and an aneurysm of that size must have produced distress. In the absence of any constitutional symptoms pyopneumothorax can be excluded."

From a diagnostic and physical point of view it is obviously of little importance what the medium is through which pulsation takes place, as long as it is fluid. Certainly from the roentgenologist's standpoint it is important.

In both these cases fairly definite signs of pulmonary tuberculosis were present, and, as is well known, tuberculosis is the primary cause of this interesting condition in the majority of cases.

I am indebted to Dr. George Blumer and Dr. Wilder Tileston for these cases, on whose services they occurred.

ASTHMA COMPLICATING THE SERUM TREATMENT OF PNEUMONIA *

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As the use of antipneumococcus horse serum becomes more extensive, cases are met with wherein sensitiveness to serum complicates its administration, as happens with the therapeutic use of other serums. The reaction induced by giving horse serum to such patients may vary, depending on several factors, among which is liability to "horse asthma." Patients with this condition complain that proximity to horses, whether currying them, driving them, or even going into stables, may bring on symptoms which are typical of bronchial asthma, due doubtless to suspended particles of horse dandruff or horsehair. Walker[1] has found that most patients suffering from this condition give positive cutaneous reactions to horsehair proteins, whereas in addition a much smaller number (22 per cent.) react to horse serum proteins. Woodehouse[2] has established the fact that the fractional portions of the protein mixture hair, may sensitize, or rather, that its administration results in multisensitization to its individual proteins. Similar reactions have been demonstrated in plant proteins by Lake, Wells and Osborne,[3] and others. On the other hand, it is questionable whether any one protein of hair is identical with any protein of serum, although it will be shown that a close relationship exists.

At the Peter Bent Brigham Hospital where, during the past winter, antipneumococcus serum was administered to fifteen patients with Type I[4] infection, three cases were encountered in each of which there was a definite history of "horse asthma." This is a higher incidence than has been met with either at the Hospital of the Rockefeller Institute, from which we obtained our serum through the courtesy of Dr. Cole, or at the Presbyterian Hospital, New York, where serum has been used extensively. It is appreciated that so small a number of cases as here reported forbids conclusive deductions, and the value attributed to the cases lies rather in their constant manifestations and

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* Submitted for publication July 12, 1917.

* From the Medical Service of the Peter Bent Brigham Hospital.

1. Walker, I. C.: Jour. Med. Research, 1917, **35,** 497.

2. Woodehouse, R. P.: Jour. Immunol., 1917, **2,** 237.

3. Lake, G. C.; Wells, H. G., and Osborne, T. B.: Jour. Infect. Dis., 1914, **14,** 364, 377; 1915, **17,** 259.

4. Cole, Rufus: Treatment of Pneumonia by Means of Specific Serums, Jour. Am. Med. Assn., 1913, **61,** 663.

in the experience gained in giving considerable quantities of serum to such patients. Antipneumococcus serum is used in large doses, 90 c.c. or more, intravenously, which far exceeds the amounts ordinarily used of other serums.

A cutaneous test, similar to the von Pirquet test, with whole dried serum protein with the addition of a little tenth-normal sodium hydroxid to dissolve it, was made on all patients before treatment. Of the three asthmatic patients, but one reacted positively. A cutaneous test with horsehair protein was also made on this patient before treatment and was found to be positive, whereas it was made after treatment in the other two, and was likewise positive in each. Treatment with serum did not induce a positive cutaneous reaction to horsehair in several of the nonasthmatic individuals tested at varying intervals, and so it may be assumed that all these asthmatic patients would have given a positive skin reaction to horsehair if tested before treatment with antipneumococcus horse serum. On the other hand, the history of asthma was definite enough in each instance to demand caution in administering serum. It was not determined whether the intracutaneous test, far more sensitive than the cutaneous, made with serum would be positive in the cases reacting to horsehair.

REPORT OF CASES

CASE 1.—J. C., a man aged 25, formerly a teamster, gave a family history of asthma in that his father and two brothers suffer with it. The patient has had attacks of asthma off and on for fifteen years. He could drive horses but could not groom them. The onset of the present illness dated four days before admission with a chill, pain in the right chest, cough and fever, which persisted. He was admitted Jan. 11, 1917, with a temperature of 103.8 and signs of consolidation in the right upper lobe. Type I pneumococcus was isolated from his sputum. The cutaneous test with horse serum protein was negative. One c.c. of horse serum was given subcutaneously one hour before treatment, without reaction. Anti-pneumococcus Serum I diluted with equal parts of physiologic sodium chlorid solution was allowed to run slowly into a vein of the arm. When about 70 c.c. of serum (140 c.c. of the mixture) had been injected, the patient's face suffused quickly, his eyes watered, respirations began to be labored and rapid, and he complained of a sense of tightness in his chest. The infusion was discontinued at once. Auscultation revealed loud asthmatic breathing. A typical attack of bronchial asthma soon developed, lasting about one-half hour, which was partially controlled by epinephrin. No further symptoms developed. His temperature fell to normal and further treatment with serum was not necessary.

January 26: Cutaneous tests were made with the proteins of doghair, cathair, rag weed, golden rod, corn, grass, poplar leaves, maple leaves, *Staphylococcus albus, Staphylococcus aureus,* and *Bacillus diphtheroidae,* all of which were negative. Red top was positive, horsehair was positive. The component proteins of hair gave negative reactions with alkali-metaprotein, and coagulated protein, whereas peptone was positive in dilutions of 1:100 and 1:1,000.

CASE 2.—H. B., aged 42, formerly a fireman, had been subject to asthma for fifteen years. This was induced by horses and hay dust in the fire house and aggravated by smoke. He was admitted Feb. 6, 1917. His present illness

began three days before with a chill, fever and cough. On admission his temperature was 104; no pathologic signs were found in the lungs on physical examination but a roentgenogram revealed a central consolidation of the left lower lobe. Type I pneumococcus was isolated from his sputum. Cutaneous tests with horse serum and horsehair proteins were strongly positive.

In an attempt to desensitize to horse serum, the procedure was as follows:

February 7, 2:20 p. m., 0.25 c.c. antipneumococcus serum subcutaneously; violent asthma in fifteen minutes, lasting twenty minutes.

3:30 p. m., 0.025 c.c. antipneumococcus serum subcutaneously. No reaction.

4:15 p. m., 0.066 c.c. antipneumococcus serum subcutaneously. No reaction.

4:45 p. m., 0.1 c.c. antipneumococcus serum subcutaneously. No reaction.

5:15 p. m., 0.25 c.c. antipneumococcus serum subcutaneously. No reaction.

5:30 p. m., 0.5 c.c. antipneumococcus serum subcutaneously. No reaction.

6:00 p. m., 1 c.c. antipneumococcus serum subcutaneously. Urticaria over entire body.

8:00 p. m., 2 c.c. antipneumococcus serum subcutaneously. Urticaria fading.

8:30 p. m., 1 c.c. antipneumococcus serum intravenously. Nausea, vomiting, violent asthma in ten minutes.

10:00 p. m., 1 c.c. antipneumococcus serum intravenously. Nausea, vomiting; no asthma.

11:10 p. m., 2 c.c. antipneumococcus serum intravenously. No reaction.

12:00 m., 4 c.c. antipneumococcus serum intravenously. No reaction.

February 8, 12:45 a. m. Antipneumococcus Serum I with equal parts of saline was allowed to run slowly into a vein. After 70 c.c. of serum (140 c.c. of the mixture) had been given, the face became suffused, eyes watered, and patient complained of "itching all over." Infusion was discontinued. Within ten minutes there were nausea and vomiting but no asthma developed.

12:00 m. Temperature 99. Cutaneous tests with horse serum and with horsehair protein were negative.

8:00 p. m. Temperature 101.4. One c.c. of antipneumococcus serum was given intravenously. There was no reaction.

9:15 p. m. Antipneumococcus serum and saline were infused slowly. When 65 c.c. of the serum had run in, the face became suffused, and eyes began to water; treatment was stopped. In ten minutes an asthmatic attack began lasting fifteen minutes. There was no further reaction.

February 9. Temperature 99. Cutaneous test with horsehair protein negative. Horse serum protein negative.

February 13. Cutaneous test with horsehair protein slightly positive. Horse serum protein negative.

February 16. Cutaneous test with horsehair protein moderately positive. Horse serum protein negative.

February 20. Cutaneous test with horsehair protein moderately positive. Horse serum protein negative.

February 23. Cutaneous test with horsehair protein moderately positive. Horse serum protein negative. Proteins of timothy and red top negative.

February 26. Cutaneous test with horsehair protein strongly positive. Horse serum protein negative.

February 28. Cutaneous test with horsehair protein moderately positive. Horse serum protein negative. Cutaneous test with horsehair alkali-metaprotein, 1:100, positive; 1:1,000, positive; 1:10,000, negative.

May 1. Cutaneous tests with horsehair alkali-metaprotein and peptone were positive in dilutions to 1:1,000. Those with whole horse serum protein, serum albumin, euglobulin, and pseudoglobulin, were all negative. The patient has been working as a chauffeur and gasoline vapor causes a little difficulty in breathing, but there has been no typical asthma.

Case 3.—H. R., aged 37, was fond of horses and did considerable driving about ten years ago, but was compelled to give this up because it caused water-

ing of the eyes, sneezing and some difficulty in breathing. He had not been similarly affected since. The present illness began four days before serum treatment with a chill, pain in the right chest, and fever. May 6, 1917, signs of consolidation were found over the entire right lung. May 7, pneumococcus, Type I, was isolated from the sputum. Temperature 103; patient was very ill. Cutaneous test to horse serum, negative; 0.25 c.c., 0.5 c.c. and 1 c.c. of serum were given subcutaneously, then 0.5 c.c. and 1 c.c. intravenously, at fifteen minute intervals, but no reaction whatever was noted. Intravenous infusion with serum diluted with saline was begun. When about 40 c.c. of serum had been administered, the patient's face rapidly flushed, and treatment was stopped. In a few minutes he became restless and had an asthmatic attack which persisted for one-half hour. Eight hours later serum was again infused without attempted desensitization. After 40 c.c. had run in, a reaction similar to that after the first treatment occurred. Six and a half hours later, serum was given, and 60 c.c. were tolerated before a mild reaction occurred. Another injection eight and one-half hours later brought on a mild reaction after 65 c.c. of serum had been given. A fifth infusion was administered after six hours, and 75 c.c. of serum were tolerated before a mild reaction occurred. In six hours another serum treatment was given, and 70 c.c. injected when a moderate reaction appeared. The patient was extremely ill, and the pneumonic process had extended into the left lower lobe. He rallied after the last infusion and became progressively better thereafter. A cutaneous test with horsehair protein on June 16 gave a strongly positive reaction; that with horse serum was negative.

COMMENT

From these cases it is apparent that there is a distinct difference in the reaction to horse serum infusion, depending on whether the individual is sensitized to hair, or to both serum and hair. In the first instance, desensitization with small amounts of serum seems to be of no avail, as it requires a considerable quantity, 40 c.c. or more, to produce a reaction. In that most patients with "horse asthma" may be easily desensitized with small amounts of horsehair protein,[5] it is quite likely that such desensitization would have averted the reactions induced by large amounts of serum. In all the cases, the cutaneous test to horsehair persisted long after treatment, excepting the immediate desensitization, which was but transient, in Case 2. On the other hand, the reaction to horse serum protein was in no instance positive after treatment.

In none of these cases were there evidences of serum sickness, excepting a few doubtful changes in Case 3. This patient had moderate soreness of his temperomaxillary joints for one day and a little difficulty in breathing twelve days after the last serum injection. This contrasts sharply with the nonasthmatics in whom manifest serum sickness of more or less severity occurred in almost every case.

The reaction brought about only by large amounts of horse serum has not been studied. Obviously, it is anaphylactic. Wells and Osborne[6] maintain that the specificity of the anaphylaxis reaction is

5. Walker, I. C.: Jour. Med. Research, 1917, **36**, 243.
6. Wells, H. G., and Osborne, T. B.: Jour. Infect. Dis., 1913, **12**, 341.

determined by the chemical structure of the reacting proteins rather than by their biologic origin, and that the entire protein molecule is not involved in the specific character of the reaction, but this is developed by certain structural groups contained therein. Consequently, it is possible that such a group of one of the proteins of the serum may be identical with a group of the hair, to which the patient is sensitized, and as serum is introduced, the action of this group remains subliminal until a quantity, usually large, has been administered, sufficient to cause symptoms. Another explanation is in accordance with the work of Manwaring and Kusama.[7] They perfused the lungs of guinea-pigs which had been immunized by frequent injections of goat serum with the blood of these guinea-pigs and goat serum, and thereby demonstrated a coincident fixed cellular hypersensitiveness and humeral immunity. Dale[8] had previously demonstrated the occurrence of cellular hypersensitiveness. It is conceivable that in the above patients such an excess of serum was given that their blood no longer protected, and hypersensitiveness of the tissues became manifest.

SUMMARY

Pneumonia patients with "horse asthma" reacted differently to infusions of antipneumococcus serum, depending on whether they were sensitive to horsehair and horse serum, or to horsehair alone. In the first instance, not even small subcutaneous injections of serum could be tolerated, whereas in the latter, no reaction occurred until considerable quantities of serum had been given, although the cutaneous test with serum had been negative. This suggests a close relationship between one or more of the horse serum proteins and those of horsehair.

Patients sensitive either to serum or hair could be desensitized so that eventually doses of serum sufficient to produce a curative effect on the pneumonic process were given. Therefore, asthma apparently does not contraindicate the employment of antipneumococcus serum.

There were few or no manifestations of serum sickness in asthmatic patients, even after as much as 350 c.c. of antipneumococcus horse serum had been infused, whereas in nonasthmatic patients, serum sickness almost always occurred.

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7. Manwaring, W. H., and Kusama, Y.: Jour. Immunol., 1917, **2**, 157.
8. Dale, H.: Jour. Pharm. and Exper. Therap., 1912, **4**, 167.